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since 1885

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September and October numbers contain papers delivered at
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Cefotan arithmetic.

+ more cost-effective than cefoxitin[1,2]

− less frequent dosing than cefoxitin[3,4]

× several times the half-life of cefoxitin[5,6]

÷ single-dose prophylaxis/ twice-daily treatment

P, 24,801

Count on

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(cefotetan disodium)

In intra-abdominal and gynecologic infection due to indicated organisms

References: **1.** Nightingale CH, Smith KS, Quintiliani R, et al: The conversion of cefoxitin usage to cefotetan: An interdisciplinary approach. *Am J Surg* 1988;155(5A):101-102. **2.** Sochalski A, Sullman S, Andriole VT: Cost-effectiveness study of cefotetan versus cefoxitin and cefotetan versus combination antibiotic regimens. *Am J Surg* 1988;155(5A):96-101. **3.** CEFOTAN® (cefotetan disodium) full prescribing information issued March 1986. **4.** *Physicians' Desk Reference*, ed 43. Oradell, NJ, Medical Economics Co, 1989. Mefoxin® (cefoxitin sodium, MSD), pp 1355-1357. **5.** Carver M, Quintiliani R, Nightingale CH: Comparative pharmacokinetic study of cefotetan and cefoxitin in healthy volunteers. *Infect Surg*, April 1986 (suppl), pp 11-14. **6.** Quintiliani R, Nightingale CH, Stevens RC, et al: Comparative pharmacokinetics of cefotetan and cefoxitin in patients undergoing hysterectomies and colorectal operations. *Am J Surg* 1988;155(5A):67-70.

Please see adjacent page for brief summary of prescribing information.

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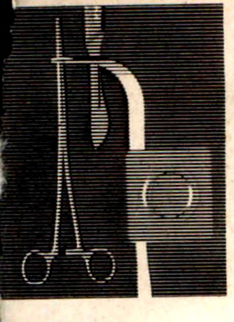

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CEFOTAN® IM/IV

(cefotetan disodium)

In intra-abdominal and gynecologic infection due to indicated organisms

For Intravenous or Intramuscular Use
BRIEF SUMMARY

INDICATIONS AND USAGE
TREATMENT: CEFOTAN® (cefotetan disodium) is indicated for the therapeutic treatment of the following infections when caused by susceptible strains of the designated organisms:
Urinary tract infections caused by *E coli, Klebsiella* species (including *K pneumoniae*), *Proteus mirabilis* and *Proteus* sp (which may include the organisms now called *Proteus vulgaris, Providencia rettgeri*, and *Morganella morganii*).
Lower respiratory tract infections caused by *Streptococcus pneumoniae* (formerly *D pneumoniae*), *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Haemophilus influenzae* (including ampicillin-resistant strains), *Klebsiella* species (including *K pneumoniae*), and *E coli*.
Skin and skin structure infections caused by *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis, Streptococcus pyogenes* and *Streptococcus* species (excluding enterococci), and *E coli*.
Gynecologic infections caused by *Staphylococcus aureus** (including penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis, Streptococcus* species (excluding enterococci), *E coli, Proteus mirabilis, Neisseria gonorrhoeae, Bacteroides* species (excluding *B distasonis, B ovatus, B thetaiotaomicron*), *Fusobacterium* species,* and gram-positive anaerobic cocci (including *Peptococcus* and *Peptostreptococcus* species*).
Intra-abdominal infections caused by *E coli, Klebsiella* species (including *K pneumoniae**), *Streptococcus* species (excluding enterococci), and *Bacteroides* species (excluding *B distasonis, B ovatus, B thetaiotaomicron*).
Bone and joint infections caused by *Staphylococcus aureus*.*
*Efficacy for this organism in this organ system was studied in fewer than ten infections.

Specimens for bacteriological examination should be obtained in order to isolate and identify causative organisms and to determine their susceptibilities to cefotetan. Therapy may be instituted before results of susceptibility studies are known; however, once these results become available, the antibiotic treatment should be adjusted accordingly.

In cases of confirmed or suspected gram-positive or gram-negative sepsis or in patients with other serious infections in which the causative organism has not been identified, it is possible to use CEFOTAN concomitantly with an aminoglycoside. Cefotetan combinations with aminoglycosides have been shown to be synergistic in vitro against many Enterobacteriaceae and also some other gram-negative bacteria. The dosage recommended in the labeling of both antibiotics may be given and depends on the severity of the infection and the patient's condition.

NOTE: If CEFOTAN and an aminoglycoside are used concomitantly, renal function should be carefully monitored, especially if higher dosages of the aminoglycoside are to be administered or if therapy is prolonged, because of the potential nephrotoxicity and ototoxicity of aminoglycosidic antibiotics. Although, to date, nephrotoxicity has not been noted when CEFOTAN was given alone, it is possible that nephrotoxicity may be potentiated if CEFOTAN is used concomitantly with an aminoglycoside.
PROPHYLAXIS: The preoperative administration of CEFOTAN may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures that are classified as clean contaminated or potentially contaminated (eg, cesarean section, abdominal or vaginal hysterectomy, transurethral surgery, biliary tract surgery, and gastrointestinal surgery).

The prophylactic dose of CEFOTAN should be administered 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, CEFOTAN should be administered intravenously after the clamping of the umbilical cord.

If there are signs and symptoms of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate therapeutic measures may be initiated.

CONTRAINDICATIONS
CEFOTAN is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS
Before therapy with CEFOTAN is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefotetan disodium, cephalosporins, penicillins, or other drugs. This product should be given cautiously to penicillin-sensitive patients. Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. If an allergic reaction to CEFOTAN occurs, discontinue the drug. Serious acute hypersensitivity reactions may require epinephrine and other emergency measures.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad-spectrum antibiotics may alter normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin in vitro.

Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated. When the colitis is not relieved by drug discontinuance, or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile*. Other causes should also be considered.

PRECAUTIONS
GENERAL: As with other broad-spectrum antibiotics, prolonged use of CEFOTAN may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection does occur during therapy, appropriate measures should be taken.

In common with many other broad-spectrum antibiotics, CEFOTAN may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment or poor nutritional state, the elderly and patients with cancer. Prothrombin times should be monitored in patients at risk and exogenous vitamin K administered as indicated.

CEFOTAN should be used with caution in individuals with a history of gastrointestinal disease, particularly colitis.

INFORMATION FOR PATIENTS: As with some other cephalosporins, a disulfiram-like reaction characterized by flushing, sweating, headache, and tachycardia may occur when alcohol (beer, wine, etc.) is ingested within 72 hours after CEFOTAN administration. Patients should be cautioned about the ingestion of alcoholic beverages following the administration of CEFOTAN.
DRUG INTERACTIONS: Although to date nephrotoxicity has not been noted when CEFOTAN was given alone, it is possible that nephrotoxicity may be potentiated if CEFOTAN is used concomitantly with an aminoglycoside.
DRUG/LABORATORY TEST INTERACTIONS: A false positive reaction for glucose in urine may occur with Benedict's or Fehling's solution.

As with other cephalosporins, high concentrations of cefotetan may interfere with measurement of serum and urine creatinine levels by Jaffe reaction and produce false increases in the levels of creatinine reported.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Although long-term studies in animals have not been performed to evaluate carcinogenic potential, no mutagenic potential of cefotetan was found in standard laboratory tests.

Cefotetan has adverse effects on the testes of prepubertal rats. Subcutaneous administration of 500 mg/kg/day (approximately 8-16 times the usual adult human dose) on days 6-35 of life (thought to be developmentally analogous to late childhood and prepuberty in humans) resulted in reduced testicular weight and seminiferous tubule degeneration in 10 of 10 animals. Affected cells included spermatogonia and spermatocytes; Sertoli and Leydig cells were unaffected. Incidence and severity of lesions were dose-dependent; at 120 mg/kg/day (approximately 2-4 times the usual human dose) only 1 of 10 treated animals was affected, and the degree of degeneration was mild.

Similar lesions have been observed in experiments of comparable design with other methylthiotetrazole-containing antibiotics and impaired fertility has been reported, particularly at high dose levels. No testicular effects were observed in 7-week-old rats treated with up to 1000 mg/kg/day SC for 5 weeks, or in infant dogs (3 weeks old) that received up to 300 mg/kg/day IV for 5 weeks. The relevance of these findings to humans is unknown.

USAGE IN PREGNANCY: Pregnancy Category B: Reproduction studies have been performed in rats and monkeys at doses up to 20 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefotetan. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
USAGE IN NURSING MOTHERS: Cefotetan is excreted in human milk in very low concentrations. Caution should be exercised when cefotetan is administered to a nursing woman.
PEDIATRIC USE: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
In clinical studies, the following adverse effects were considered related to CEFOTAN therapy.
Gastrointestinal symptoms occurred in 1.5% of patients; the most frequent were diarrhea (1 in 80) and nausea (1 in 700).
Hematologic laboratory abnormalities occurred in 1.4% of patients and included eosinophilia (1 in 200), positive direct Coombs' test (1 in 250), and thrombocytosis (1 in 300).
Hepatic enzyme elevations occurred in 1.2% of patients and included a rise in SGPT (1 in 150), SGOT (1 in 300), alkaline phosphatase (1 in 700), and LDH (1 in 700).
Hypersensitivity reactions were reported in 1.2% of patients and included rash (1 in 150) and itching (1 in 700).
Local effects were reported in less than 1.0% of patients and included phlebitis at the site of injection (1 in 300), and discomfort (1 in 500). During postmarketing experience with CEFOTAN, anaphylactic reactions and transient thrombocytopenia have been reported.

DOSAGE AND ADMINISTRATION
TREATMENT: The usual adult dosage is 1 or 2 grams of CEFOTAN administered intravenously or intramuscularly every 12 hours for 5 to 10 days. Proper dosage and route of administration should be determined by the condition of the patient, severity of the infection, and susceptibility of the causative organism.

GENERAL GUIDELINES FOR DOSAGE OF CEFOTAN

Type of Infection	Daily Dose	Frequency and Route
Urinary Tract	1-4 grams	500 mg every 12 hours IV or IM 1 or 2 g every 24 hours IV or IM 1 or 2 g every 12 hours IV or IM
Other Sites	2-4 grams	1 or 2 g every 12 hours IV or IM
Severe	4 grams	2 g every 12 hours IV
Life-Threatening	6* grams	3 g every 12 hours IV

*Maximum daily dosage should not exceed 6 grams.

PROPHYLAXIS: To prevent postoperative infection in clean contaminated or potentially contaminated surgery in adults, the recommended dosage is 1 or 2 g of CEFOTAN administered once, intravenously, 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, the dose should be administered as soon as the umbilical cord is clamped.
IMPAIRED RENAL FUNCTION: When renal function is impaired, a reduced dosage schedule must be employed. The following dosage guidelines may be used.

DOSAGE GUIDELINES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

Creatinine Clearance mL/min	Dose	Frequency
>30	Usual Recommended Dosage*	Every 12 hours
10-30	Usual Recommended Dosage*	Every 24 hours
<10	Usual Recommended Dosage*	Every 48 hours

*Dose determined by the type and severity of infection, and susceptibility of the causative organism.

Alternatively, the dosing interval may remain constant at 12 hour intervals, but the dose reduced to one-half the usual recommended dose for patients with a creatinine clearance of 10-30 mL/min, and one-quarter the usual recommended dose for patients with a creatinine clearance of less than 10 mL/min.

When only serum creatinine levels are available, creatinine clearance may be calculated from the following formula. The serum creatinine level should represent a steady state of renal function.

$$\text{Males:} \quad \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/100 mL)}}$$

$$\text{Females:} \quad 0.9 \times \text{value for males}$$

Cefotetan is dialyzable and it is recommended that for patients undergoing intermittent hemodialysis, one-quarter of the usual recommended dose be given every 24 hours on days between dialysis and one-half the usual recommended dose on the day of dialysis.

HOW SUPPLIED
CEFOTAN is a dry, white to pale yellow powder supplied in vials containing cefotetan disodium equivalent to 1 g and 2 g cefotetan activity for intravenous and intramuscular administration. The 1 g dose is available in 10 mL and 100 mL vials, and the 2 g dose is available in 20 mL and 100 mL vials. CEFOTAN is also available in a pharmacy bulk package of 10 g in 100 mL vials. The vials should not be stored at temperatures above 22°C and should be protected from light.

1 g in 10 mL vial (NDC 0038-0376-10); 2 g in 20 mL vial (NDC 0038-0377-20); 1 g in 100 mL vial (NDC 0038-0376-11); 2 g in 100 mL vial (NDC 0038-0377-21); 10 g in 100 mL vial (NDC 0038-0375-10).

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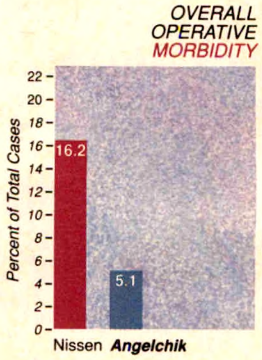

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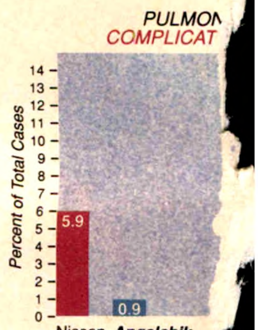

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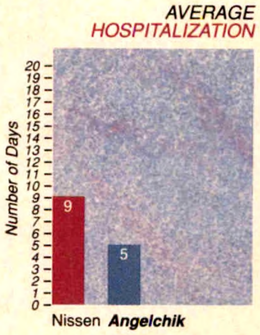

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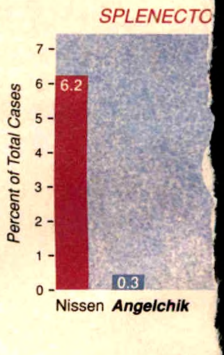

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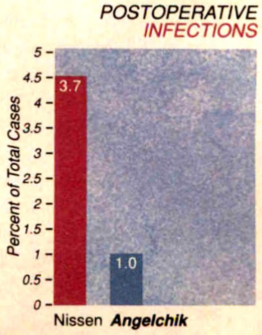

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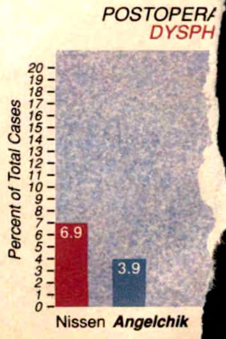

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Benign Postoperative Biliary Strictures

Operate or Dilate?

HENRY A. PITT, M.D., STEPHEN L. KAUFMAN, M.D., JoANN COLEMAN, R.N., M.S.,
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At The Johns Hopkins Hospital from 1979 through 1987, 42 patients had 45 procedures for benign postoperative biliary strictures. Three patients were managed with both surgery and balloon dilatation. Twenty-five patients underwent surgical repair with Roux-Y choledocho- or hepaticojejunostomy with postoperative transhepatic stenting for a mean of 13.8 ± 1.3 months. Twenty patients had balloon dilatation a mean of 3.9 times and were stented transhepatically for a mean of 13.3 ± 2.0 months. The two groups were similar with respect to multiple parameters that might have influenced outcome. Mean length of follow-up was 57 ± 7 and 59 ± 6 months for surgery and balloon dilatation, respectively. No patients died after any of the procedures. The same definition of a successful outcome was applied to both groups and was achieved in 88% of the surgical and in only 55% of the balloon dilatation patients ($p < 0.02$). Significant hemobilia occurred more often with balloon dilatation (20% *vs.* 4%, $p < 0.02$). The total hospital stay and cost of balloon dilatation was not significantly different from surgery. We conclude that surgical repair of benign postoperative strictures results in fewer problems that require further therapy. Nevertheless balloon dilatation is an alternative for patients who are at high risk or who are unwilling to undergo another operation.

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RECENT REPORTS[1–5] of nonoperative balloon dilatation of benign postoperative biliary strictures have been encouraging. Reported success rates for balloon dilatation have ranged from 85% to 70%, with mean follow-up periods of 24 to 36 months. These results are very similar to those reported in recent surgical series[6–10] with mean follow-up ranging from 60 to 133 months. Comparison of the results of balloon dilatation with those of surgery has been difficult, however, because of differences in techniques of dilatation and stenting at different institutions, the definition of a successful procedure, and the length of follow-up. This analysis was undertaken, therefore, to review the results of balloon dilatation and surgery at one institution over the same period of time, with similar management techniques, and the same definition of a successful outcome.

Methods

Patient Population

From January 1979 through December 1987 all patients with benign postoperative biliary strictures managed

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TABLE 1. *Patient Characteristics*

Patient Characteristics	Surgery (n = 25)	Balloon Dilatation (n = 20)
Demographics		
Age	49.2 ± 2.9	45.3 ± 4.4
Female	56%	45%
Caucasian	92%	85%
Underlying disease		
Gallstones	96%	90%
Choledochal cyst	4%	5%
Trauma	0%	5%
Associated problems		
Obstructive jaundice	48%	50%
Intrahepatic stones	32%	35%
Cirrhosis	12%	15%
Portal hypertension	8%	5%
Biliary Fistula	8%	5%

at The Johns Hopkins Hospital were evaluated. Patients with biliary strictures after surgery for biliary stones, a choledochal cyst, or trauma were included in this analysis. However two patients with severe hepatobiliary trauma requiring hepatic lobectomy plus stricture repair managed with both surgery and balloon dilatation were excluded from this report. Patients with other benign biliary strictures due to sclerosing cholangitis, chronic pancreatitis, or sphincter of Oddi stenosis were also excluded from this study. During this 8-year analysis, 42 patients with benign postoperative strictures underwent 45 procedures at John Hopkins. Twenty-five patients underwent surgical repair of their stricture, whereas 20 patients were managed with balloon dilatation. During the study period, three patients underwent both surgery and balloon dilatation. All patients were managed by both surgeons and radiologists. The choice of management technique was based on patient preference and evolving data with respect to outcome. None of the patients treated with balloon dilatation were considered to have a prohibitive risk for surgery.

Patient characteristics for the surgery and balloon dilatation groups are presented in Table 1. No differences were noted between the two groups with respect to age, sex, or race. In all but three patients (one surgery and two balloon dilatation) the underlying disease process was gallstones. Presentation with obstructive jaundice or biliary fistula and associated problems such as intrahepatic stones, cirrhosis, and portal hypertension were seen with equal frequency in the two groups. Three patients (12%) in the surgery group had right lobe atrophy and left lobe hypertrophy, whereas this atrophy/hypertrophy complex was not found in the balloon dilatation patients. A small subhepatic abscess was found at surgery in one patient.

One or more previous surgical attempts at stricture repair had been undertaken in 56% of the surgical patients and in 65% of the balloon dilatation patients (Table 2). Among the patients managed with reoperation, nine (36%) had previously undergone a biliary-enteric anastomosis, and five (20%) had end-to-end surgical repairs. All 13 patients (65%) in the balloon dilatation group with a previous surgical repair had undergone a biliary-enteric anastomosis. This trend was not statistically significant but reflected early results from this[1] and other institutions,[2,11] suggesting that results of balloon dilatation were better in patients with a biliary-enteric anastomosis.

The level of biliary obstruction in the two groups is also presented in Table 2. The level of obstruction was classified in relation to the confluence of the hepatic ducts as described by Bismuth.[12] The distribution of Types 1 to 5 was similar in the two groups. All patients were managed with transhepatic biliary stents (Table 2). Surgical patients were more likely ($p < 0.05$) than balloon dilatation patients to be managed with bilateral biliary stents. Duration of stenting, however, was similar in the two groups.

Balloon Dilatation

Access to the biliary tract was initially achieved with percutaneous transhepatic drainage. Subsequent management consisted of balloon dilatation of the stricture, postdilatation stenting, stricture challenge, and catheter removal (Fig. 1), as previously described.[1,13,14] The first balloon dilatation was usually performed a few days after percutaneous drainage while the patient was still hospitalized. Dilatations were performed with commercially available angioplasty balloon catheters. Selection of bal-

TABLE 2. *Previous Repair, Level of Obstruction, Use of Stents*

Patient Characteristics	Surgery % (n = 25)	Balloon Dilatation % (n = 20)
Previous repair		
None	44	35
One	44	55
Two	4	5
Three	4	0
More than three	4	5
Level of obstruction		
Type 1* (>2 cm CHD†)	16	25
Type 2 (<2 cm CHD)	35	40
Type 3 (bifurcation)	24	15
Type 4 (hepatic ducts)	16	15
Type 5 (right branch)	8	5
Use of stents		
Right	44	90
Left	16	5
Both	40‡	5
Time (months)	13.8 ± 1.3	13.3 ± 2.0

* Bismuth classification.[12]
† CHD = common hepatic duct.
‡ $p < 0.05$ *vs.* balloon dilatation.

loon diameter was determined by the diameter of the adjacent normal bile duct. Balloon length was determined by the length of the stricture. After balloon dilatation, the strictured segment was stented with a catheter for the next several weeks. A second balloon dilatation was then performed, usually as an outpatient, and a larger stent was placed across the stricture. This procedure was repeated during the first few months until stents as large as adjacent ducts could be passed.

The mean number of dilatations was 3.9 per patient, with a range of 1 to 11. Maximum stent size was 10–12F in 11 patients, 14–16F in 6 patients, and 18–22F in 4 patients. The larger stents were made of silastic and were the same as those used after surgery. Stents were changed routinely every 3 to 4 months. Initial stenting averaged 10 months, but this mean increased to 13.3 months (Table 2) as restrictures were redilated and stented. Four of 20 patients (20%), including two children, required general anesthesia for balloon dilations. The remaining patients received local anesthesia and intravenous analgesia and sedation. In addition to balloon dilatations, seven patients (35%) had intrahepatic stones retrieved or flushed into the intestine.

Surgery

Preoperative Ring catheters were placed into one or both hepatic ducts in 12 and six patients, respectively. These percutaneous stents were placed preoperatively in 17 of the last 20 patients. Having these catheters in place at the time of operation helped in dissecting the strictured area and subsequently placing transhepatic silastic stents as previously described.[15-17] At surgery the common bile duct was divided distally early in the dissection. This maneuver facilitated cephalad dissection and separation of the biliary tree from the portal vein. Exposure of the portal vein allowed safer dissection in the more proximal scarred area. Having Ring catheters in the right and left hepatic ducts before operation aided in the identification of these strictures above the bifurcation and facilitated further dissection of hilar strictures. Moreover resection of the stricture area revealed a traumatic neuroma in four patients (16%).

After removal of the specimen, the curved tip of the Ring catheter was cut, and a long guide wire was passed through the catheter. A 12F Coudé catheter was then passed over and sutured to the Ring catheter and pulled up through the hepatic duct and liver parenchyma. The tract was progressively dilated in this fashion until a 16F or 18F silastic stent could be positioned in the biliary tree. A Roux-Y choledocho- or hepaticojejunostomy was then performed, and the stent or stents were positioned so that the side holes were situated within the ductal system and the Roux-Y loop (Fig. 2). These silastic stents were changed routinely on an outpatient basis every 3 to 4 months and were left in for a mean of 13.8 months.

Follow-up

All 42 patients were followed until April 1989 or until death. Thus a minimum of 16 months of follow-up was available in all patients. Follow-up was obtained by review of hospital records or by telephone interview and was accomplished in all patients. Follow-up for surgery and balloon dilatation patients was 57.1 ± 6.7 months (range, 16 to 120) and 59.1 ± 5.9 months (range, 17 to 111), respectively. A successful outcome was defined as no evidence of cholangitis or jaundice requiring another procedure more than 12 months from the onset of treatment. Treatment failure was defined as the need for reoperation or dilatation, hospital death following a procedure, or late death from liver failure, biliary sepsis, or portal hypertension.

Cost Analysis

The cost of surgery and balloon dilatation were estimated from length of hospital stay and procedure charges. All calculations used charges and fees that were current for the year in which surgery was performed or balloon dilation was initiated. The cost of surgery was estimated by multiplying hospital and intensive care stay by prevailing charges and adding preoperative transhepatic drainage, surgical, and anesthesia fees, as well as the cost for postoperative stent changes. The cost of balloon dilatation was determined by multiplying total hospital stay from various admissions by prevailing charges and adding the cost of initial percutaneous transhepatic drainage, as well as multiple balloon dilatations, general anesthesia, when employed, and stent changes. The cost of major complications such as reoperation for subphrenic abscess or arteriogram and embolization for hemobilia were also included. Moreover the cost of reoperation or balloon dilatations of recurrent strictures was added to the cost of the initial procedure.

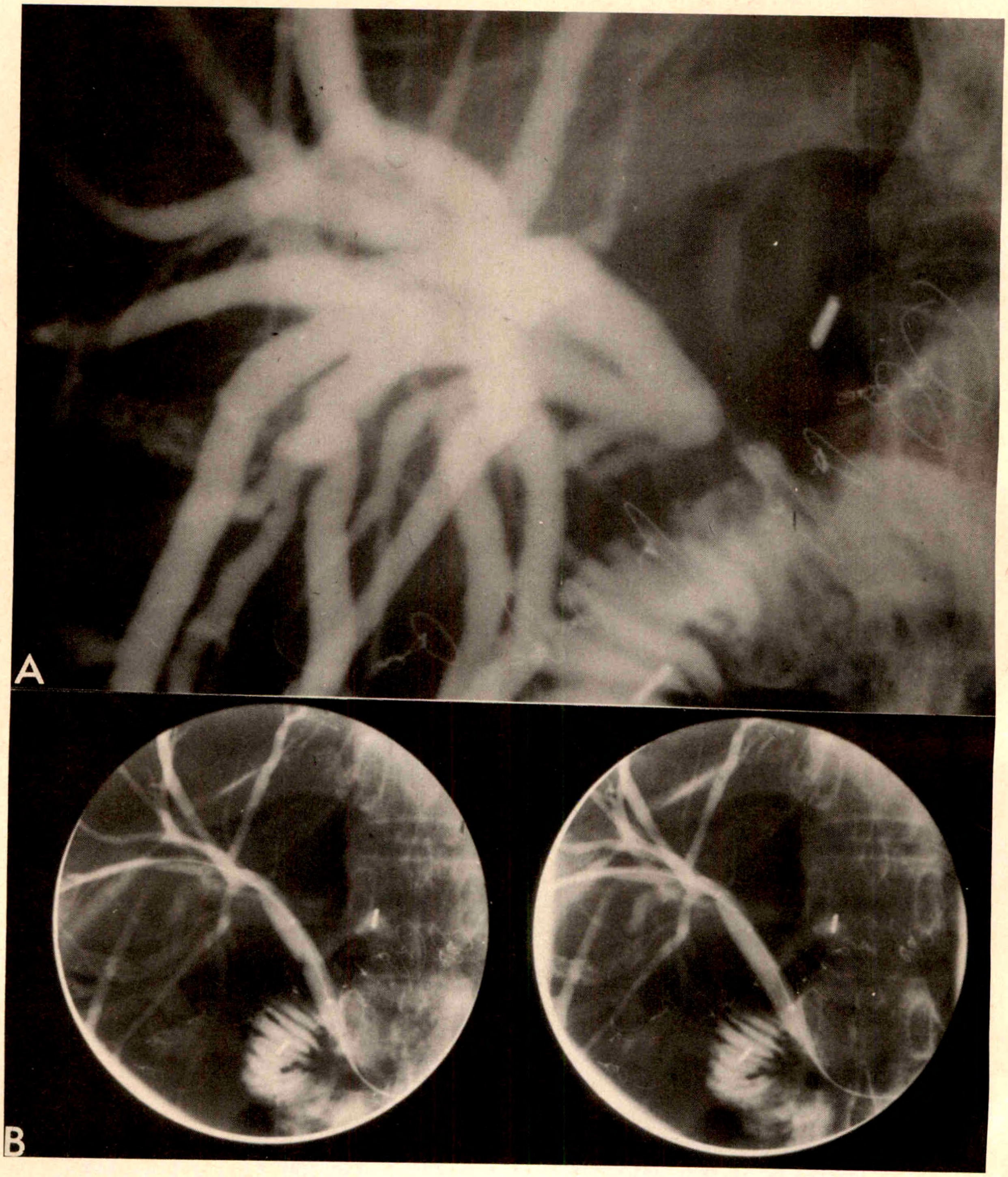
Statistical Analysis

All data are presented as mean ± standard error of the mean. Student's unpaired t test was used to compare mean age, length of stenting, hospital stay, and cost. Other patient characteristics and outcome data were compared by chi square analysis. Actuarial success rates were analyzed by the Mantel-Cox technique.

Results

Stricture Outcome

A successful outcome was achieved in 88% of the surgery and in 55% of the balloon dilatation patients (p



FIGS. 1A–D. (A) Transhepatic cholangiogram demonstrating stricture at the previous choledochojejunostomy (Bismuth type 1). (B) Progressive dilatation of the strictured anastomosis with an angioplasty balloon catheter. (C) Postdilatation stenting of the anastomotic stricture for prolonged periods. (D) Subsequent cholangiography demonstrating resolution of the anastomotic stricture.

< 0.02, Table 3, Fig. 3). Of the 25 patients managed surgically, recurrent strictures occurred in three (12%) at 20, 30, and 78 months. Two of these three patients had undergone multiple previous attempts at surgical repair. One of these patients was subsequently managed successfully with balloon dilatation, and a second patient is presently

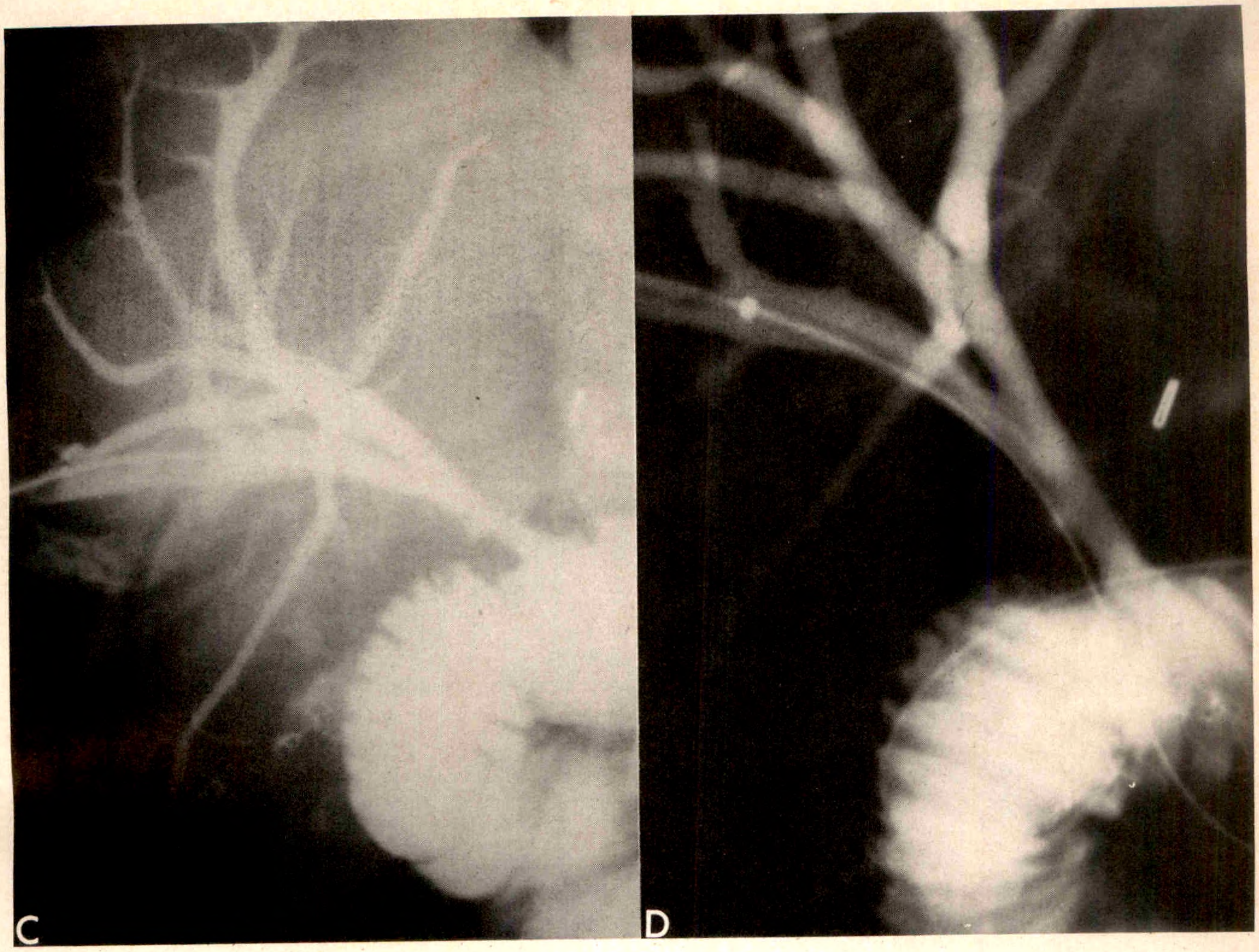
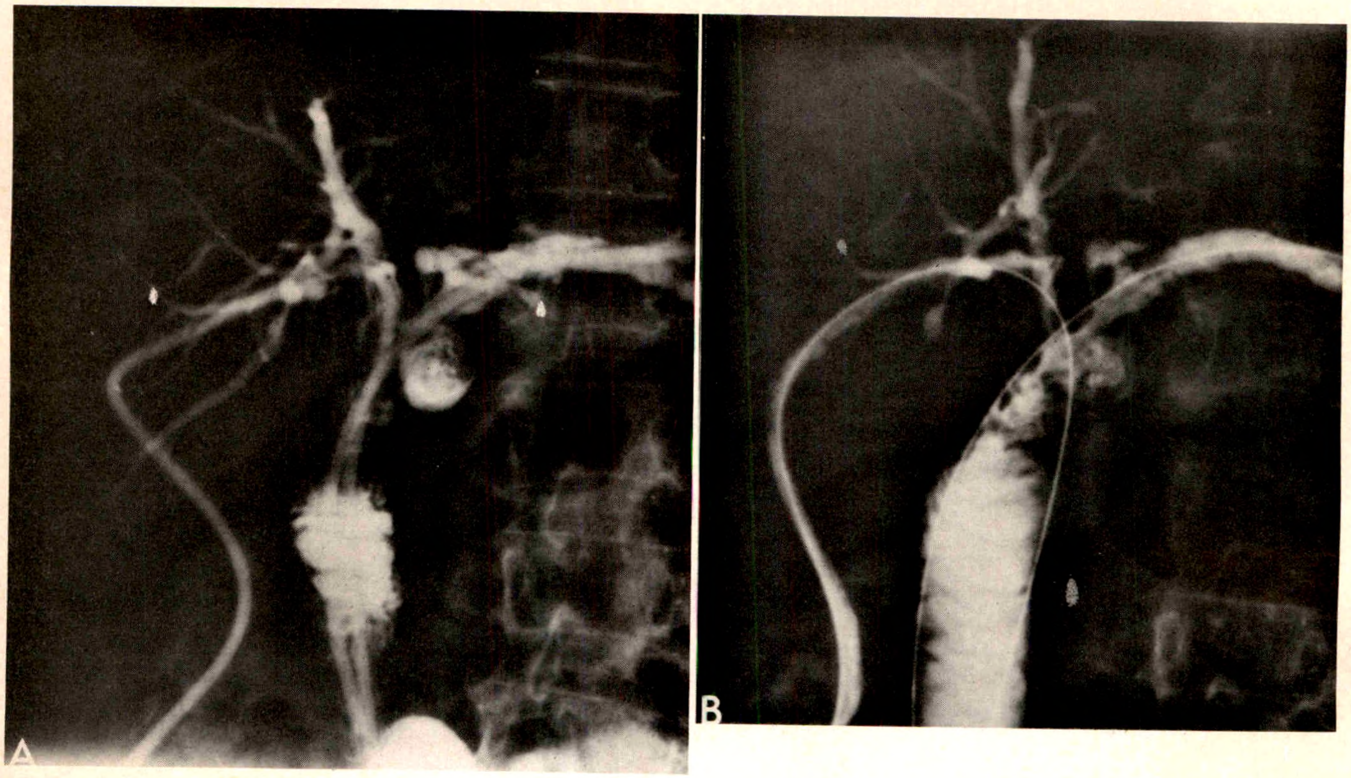


FIG. 1. (*Continued*)

undergoing this treatment. The third patient has also been managed with balloon dilatation but failed that treatment after 34 months. She was retreated with balloon dilatation beginning 15 months ago and has had her stent out now for 2 months. At latest follow-up all surgically managed patients were free of cholangitis and jaundice.

Nine of the 20 patients (45%) managed with balloon dilatation have developed recurrent strictures. All of these nine recurrent problems became apparent within 36 months of the initiation of balloon dilatation (Fig. 3). Three of these nine patients, who restrictured at 13, 16, and 27 months, underwent subsequent surgical repair 52, 14, and 7 months ago. Each of these three patients are presently well, and the first two patients have had their stents removed 40 and 2 months ago, respectively. Of the nine patients with recurrence, five restrictured at 12, 12, 15, 24, and 34 months and were managed with further balloon dilatation and prolonged stenting. Two of these five patients had their stents removed after 30 and 38 months and have been well for 59 and 11 months, respectively. The other three of these five patients have been stented continuously for 85, 49, and 45 months. The final patient, managed initially with surgery and described above, underwent repeat balloon dilatation. At last follow-up only one balloon dilatation patient, who also has Gilbert's disease, was jaundiced.

In addition to surgical management, two other factors, the type of stricture and the level of obstruction, correlated with a successful outcome (Table 3). The 22 patients with a primary stricture were significantly more likely to have a good outcome than the 23 patients with anastomotic strictures (86% *vs.* 61%, $p < 0.05$). This same trend was present when the 17 patients with no previous attempt at surgical repair were compared with the 28 patients who had undergoing a biliary-enteric or end-to-end anastomosis (82% *vs.* 68% success). This difference, however,



FIGS. 2A and B. (A) Postoperative tube cholangiogram *via* bilateral transhepatic stents demonstrating individual hepaticojejunostomies after resection of stricture (Bismuth type 4). (B) Subsequent cholangiographic assessment demonstrating patent anastomoses.

did not achieve statistical significance. All nine patients with a Bismuth type 1 stricture had a successful outcome compared to a 67% success rate for the remaining 36 patients with more complex strictures ($p < 0.05$, Table 3). Other potential risk factors such as age, sex, race, presentation with jaundice, intrahepatic stones, or cirrhosis did not correlate with outcome.

Morbidity and Mortality Rates

Morbidity and mortality data are presented in Table 4. Significant hemobilia requiring transfusion was the most frequent complication and occurred more often in patients managed with balloon dilatation (20% *vs.* 4%, $p < 0.02$). All four balloon dilatation patients with hemobilia required arteriography and embolization to control hemorrhage. The one surgical patient's bleeding subsided spontaneously. Pancreatitis, defined as an elevation of serum amylase greater than two times normal with typical clinical signs and symptoms, occurred in three patients, one postoperatively and two after balloon dilatation. After surgery two patients had bacteremias with organisms also isolated from bile, and this complication occurred once in patients managed by balloon dilatation. One surgical patient developed a subphrenic abscess that required reoperation for drainage. Overall procedure-related mor-

TABLE 3. *Factors Influencing Outcome*

Factors	Successful Outcome
Surgery *versus* dilatation	
Surgery	88%*
Balloon dilatation	55%
Type of stricture	
Primary	86%†
Anastomotic	61%
Level of stricture	
Type 1‡ (>2 cm CHD§)	100%‖
Type 2 (<2 cm CHD)	59%
Type 3 (bifurcation)	87%
Type 4 (hepatic ducts)	71%
Type 5 (right branch)	33%

* $p < 0.02$ *versus* balloon dilation.
† $p < 0.05$ *versus* anastomotic.
‡ Bismuth classification.[12]
§ CHD = common hepatic duct.
‖ $p < 0.05$ *versus* Types 2–5.

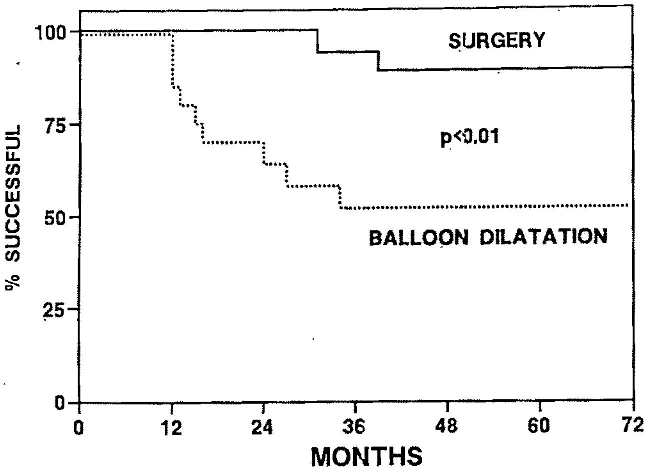


FIG. 3. Actuarial success rates over 72 months for surgery (89%) and balloon dilatation (52%). The difference is statistically significant ($p < 0.01$).

bidity was higher for balloon dilatation (35% *vs.* 20%), but this difference was not statistically significant.

None of the patients died while hospitalized following surgery or balloon dilatation (Table 4). Four of the 42 patients (10%) have died during follow-up. One late death occurred in the surgical group whereas three deaths followed balloon dilatation (4% *vs.* 15%, $p < 0.02$). One 74-year-old surgical patient died 46 months after operation of unrelated causes. Two of the late deaths in the balloon dilatation patients also occurred in elderly patients (ages 75 and 64) of unrelated causes at 46 and 86 months. The third late death after balloon dilatation was caused by a perforated gastric ulcer with generalized peritonitis. This 36-year-old patient had secondary biliary cirrhosis, but her stent had been out for 39 months without problems when she became ill. Therefore she was considered to have had a successful outcome from her balloon dilatation.

Cost Analysis

Initial hospitalization was longer for surgery than for balloon dilatation. However when rehospitalization for further dilatations, complications, and recurrences were considered, total hospital stay did not differ significantly (Fig. 4). Mean total hospital stay for surgery was 26.4 ± 2.5 days and for balloon dilatation it was 21.4 ± 1.7 days. Moreover since 1984 mean total hospital stay for surgery was down to 17.9 ± 1.5 days compared to 21.2 ± 1.7 days for balloon dilatation. Cost data paralleled hospitalization data and did not differ significantly between groups (Fig. 4). Estimated total cost for surgery was \$20,988 ± \$1376 and for balloon dilatation was \$17,728 ± \$1688.

TABLE 4. *Morbidity and Mortality*

Morbidity and Mortality	Surgery % (n = 25)	Balloon Dilatation % (n = 20)
Procedure morbidity		
Hemobilia	4	20*
Pancreatitis	4	10
Bacteremia	8	5
Subphrenic abscess	4	0
Total	20	35
Hospital mortality	0	0
Late deaths	4	15*

* $p < 0.02$ *versus* surgery.

Discussion

From 1979 through 1987, 25 patients underwent surgical repair with Roux-Y choledocho- or hepaticojejunostomy while 20 patients had balloon dilatation a mean of 3.9 times at The Johns Hopkins Hospital. Both groups of patients were managed with prolonged transhepatic stenting. Mean length of follow-up was 57 ± 7 and 59 ± 6 months for the surgery and balloon dilatation groups, respectively. No patients died after any of the procedures. A successful outcome was achieved in 88% of the surgical and in only 55% of the balloon dilatation patients ($p < 0.02$). Significant hemobilia occurred more often with balloon dilatation (20% *vs.* 4%, $p < 0.02$). Because of repeated hospitalization and procedures, the total hospital stay and cost of balloon dilatation was not significantly different from surgery.

In this retrospective analysis, the surgery and balloon dilatation groups were amazingly similar with respect to age, sex, race, initial biliary pathology, associated problems, number of previous attempts at surgical repair, and level of biliary obstruction. Relatively more balloon di-

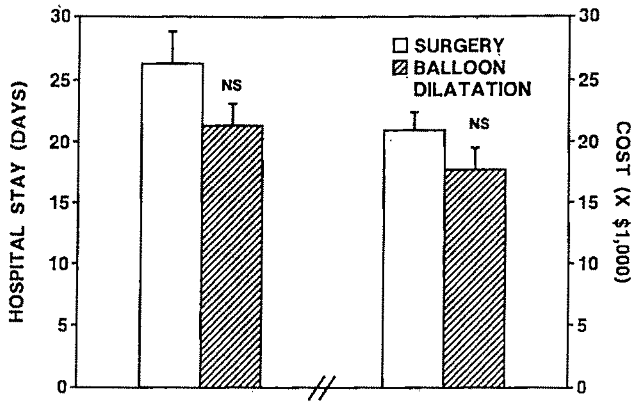


FIG. 4. Total hospital stay (left) and cost (right) for surgery and balloon dilatation. Differences were not statistically significant (NS).

latation patients had undergone a biliary-enteric anastomosis because early reports[1,2,11] suggested that results were best in these patients. The relative incidence of this subgroup of patients, however, was not statistically different between the two groups.

One important advantage of this analysis over previous reports is that all surgical and balloon dilatation patients were managed at one institution by one group of radiologists and surgeons. As a result certain techniques such as the method of percutaneous drainage, the types of stents used, the philosophy of stenting, and the assessment of results were standardized. Even the definition of a successful procedure as "no evidence of cholangitis or jaundice requiring another procedure more than 12 months from the outset of treatment" was agreed on among the authors before this series was analyzed. This definition is very similar to that recently reported by Trambert et al.[18] who "considered treatment successful if patients remained stricture-free after one biliary balloon dilatation cycle." In comparison, Muller et al.[3] chose patency at 36 months as their end point, thereby ignoring late restrictures. Moreover, Williams and his colleagues[4] judged success as "the absence of recurrent symptoms following stent removal," which creates a problem with data analysis if stents are left in place for prolonged periods.

Another advantage of this study over previous reports of balloon dilatation is the length of follow-up. Both Pitt et al.[6] and Pellegrini and his associates[9] have demonstrated that prolonged follow-up is necessary to determine the true recurrence rate after surgical repair. In both of these analyses approximately 80% of recurrent strictures developed after five years, but late recurrences were observed for up to 20 years after surgery. Thus success rates for balloon dilatation[1–5] of 85% to 70% at 2 to 3 years would be expected to decrease with longer follow-up. The mean follow-up of 59 months for balloon dilatation in this study is the longest yet reported and explains, at least in part, the lower, 55%, success rate.

In this study, in addition to surgical repair, a primary, as opposed to an anastomotic, stricture correlated with a good outcome (86% *vs.* 61%, $p < 0.05$). Three early reports[1,2,11] with a total of 21 patients with strictured biliary-enteric anastomoses suggested that balloon dilatation was successful in 90%. However recent reports[3–5] from several institutions confirm the present observation that primary strictures do better with balloon dilatation. Mueller et al.,[3] reporting data on 61 patients with postoperative strictures from four institutions, found that success rates at 36 months for primary and anastomotic strictures were 76% and 67%, respectively. Similarly Williams and his Mayo Clinic associates[4] found success rates at 28 months of 88% for primary and 73% for anastomotic strictures. Finally Moore et al.[5] at Duke reported a successful outcome at 33 months of 86% and 82% for primary and anastomotic strictures, respectively.

Endoscopic balloon dilatation of benign strictures has also been proposed. This technique, however, has the potential disadvantages of only being possible for primary strictures or choledochoduodenal anastomoses and requiring repeat endoscopies for endoprosthesis change if an indwelling stent is employed. Kiil et al.[19] from Denmark have reported successful endoprosthesis placement in 33 of 36 patients (92%) with benign strictures. Unfortunately no follow-up data are provided in this report, which focuses largely on patients with malignant obstruction. Huibregtse et al.[20] from the Netherlands also reported successful endoprosthesis placement in 27 of 29 patients (93%) with benign strictures. Clinical follow-up for at least 6 months in 23 patients suggested an excellent or good result in 19 (83%). However intubation of proximal strictures was difficult, follow-up was short, and one endoscopic failure died of sepsis after percutaneous transhepatic cholangiography. Moreover Foutch and Sivoh[21] reported two hospital deaths, a respiratory arrest, and a common bile duct perforation among nine patients with benign strictures managed endoscopically.

Another method for managing these patients is intermittent postoperative balloon dilatation through a choledochojejunocutaneous or subcutaneous fistula.[22–24] To date this technique has been used most often in patients with sclerosing cholangitis. However in two recent reports[23,24] a total of eight patients with benign postoperative strictures have been managed in this fashion with success claimed in six over a short follow-up period. With this technique no internal or external tubes were required and dilatation intervals were longer than in the present study. Presently more data are necessary to adequately evaluate this treatment modality. The most recent modification of this technique reported by Maroney and Ring[25] is percutaneous transjejunal catheterization of Roux-Y biliary-enteric anastomoses. This method does not require a cutaneous or subcutaneous fistula and may become an option in highly selected patients.

As with balloon dilatation by whatever route, the length of follow-up remains a key element in comparing the results of surgical stricture repair. Recent reports from the University of California at Los Angeles[6] and the Cleveland Clinic,[7] both with a mean follow-up of 60 months, document a successful outcome after surgery in 86% and 82% of patients, respectively. Thus the 88% success rate at 57 months in the present series is comparable to these reports. Analyses from the Lahey Clinic[8] and the University of California at San Francisco (UCSF)[9] report a successful outcome in 78% of patients at 64 and 102 months, respectively. Perhaps the longest follow-up data come from the St. George's Hospital in London where a successful outcome has been documented in 72% of patients at 133 months.

Debate continues as to the optimal surgical approach and the use and length of stenting. Some authors[12,26–28] advocate no stents with various surgical approaches to the left hepatic duct. One recent report from Ohio State[26] documents an 87% success rate in 22 patients with a mean follow-up of 72 months. However in the Hammersmith series[27] success was achieved in only 79% of 72 patients at 40 months. Advocates of a relatively short period (1 to 3 months) of stenting at the Cleveland Clinic[7] and UCSF[9] have reported success rates of 82% and 78% at 60 and 102 months, respectively. An early report[29] of the mucosal graft technique suggested a 90% success rate; but as follow-up has been extended to 11 years, this figure has decreased to 72%.[10] Finally advocates[6,15,30] of prolonged transhepatic stenting (12 to 24 months) have consistently reported success rates of 88% to 90% at 5 years as reported in this analysis.

The debate about the optimal surgical and nonsurgical treatment of these patients will undoubtedly continue unless properly designed randomized studies are performed. Until such studies are undertaken, this analysis and review of the literature suggests that surgical repair of benign postoperative strictures results in fewer problems with cholangitis or jaundice that require further therapy. Because of the need for multiple procedures and the high recurrence rate, the cost of balloon dilatation is similar to that of surgery. Nevertheless balloon dilatation is an alternative for patients who are at high risk or are unwilling to undergo another operation.

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DISCUSSION

DR. WILLIAM P. LONGMIRE, JR. (Los Angeles, California): Although, as Dr. Pitt and Dr. Cameron state, their patients have not been randomized, the long-term results achieved by the same team members and using the same evaluation criteria are interesting and important.

Many surgeons of my era remember cases in which bile duct strictures were dilated at the time of surgical exploration. This was a fairly routine treatment at the beginning of my surgical career, and it was the almost-uniform failure of such procedures that led us to persist in efforts to develop more definitive methods of operative repair. With this background experience, it is natural that many surgeons have greeted the reports of percutaneous and endoscopic dilation of these strictures with some skepticism. The present report does put the status of dilation in perspective and presents it as an avenue of treatment available primarily for patients unfit for operation.

The improved current results of dilation, as compared to those previous operative attempts, seem to have been achieved by (1) repeated bouts of dilation and, (2) prolonged stenting, an observation that may give some support to those of us who recommend prolonged stenting after surgical repair. We must certainly appreciate the authors' clear analysis of the indications for dilation and their observation of the long-term results that may be anticipated from these two methods of treatment.

DR. ROBERT E. HERMANN (Cleveland, Ohio): I appreciate the opportunity that Dr. Pitt and his colleagues have given me to discuss this paper, which I think provides important and informative data from one institution in regard to the long-term results of balloon dilation for strictures of the bile duct. They have compared these results to their results after surgical resection and repair of strictures, and to the results obtained by others.

Our results with balloon dilation of strictures, as reported to me by Dr. Mike Geisinger of our department of radiology, confirms these findings of a long-term success rate of only slightly more than 50%. However a success rate of even 50% for some of these difficult recurrent strictures is not bad as long as the morbidity of the procedure is minimal.

In Dr. Pitt's experience, four of their patients developed significant hemobilia requiring transfusion and two patients developed pancreatitis, the major complications they saw from balloon dilation. In our experience hemobilia has not occurred quite so often and seems to come as a late result of long-term catheter stents that will tend to erode through the wall of the duct into an adjacent vessel. We prefer surgical repair for most strictures, but I believe there is a place for balloon dilation. We would use it for patients previously operated on who have a recurrent single duct stenosis. That is, only one duct develops a recurrent stricture while the other remains patent. This usually leads to intermittent cholangitis only, but not jaundice.

A second indication would be for poor-risk patients with recurrent strictures, as indicated by Dr. Pitt and his colleagues, patients with cirrhosis and ascites, cardiorespiratory problems, or renal failure.

A third indication would be patients in whom the surgeon can anticipate a technically difficult operation or, more precisely, reoperation, patients who have had multiple previous operations that have failed, morbidly obese patients, and so on. In this group we would probably give balloon dilation a trial.

I wonder if Dr. Pitt has formulated a similar set of indications in his mind. When would he choose balloon dilation over operative repair? Also I would like to ask him to tell us when the patients in their series who had hemobilia bled. Did bleeding occur after the initial liver puncture and catheterization, after a dilation procedure, or late from the eroding effects of an indwelling stent?

DR. R. SCOTT JONES (Charlottesville, Virginia): I thoroughly enjoyed this presentation by Dr. Pitt. I think he and his colleagues have done an excellent job of analyzing this material and bringing the results of these two methods into perspective.

The question that I wanted to pose was outlined just a few minutes ago by Dr. Hermann, but I will repeat it anyway. I wanted to ask Dr. Pitt to tell us what algorithm he would recommend now for the integration of these two techniques, balloon dilatation and surgical treatment. When would he recommend balloon dilatation as the primary treatment? When would he avoid it, and vice versa for surgical treatment?

The other question I wanted to pose related to something not mentioned in the study, but I think it merits discussion. Sometimes patients with bile duct strictures develop multiple strictures and in some cases develop strictures of the lobar ducts or intrahepatic ducts, and I wonder if he would comment on the use of balloon dilatation in management of those difficult intrahepatic strictures.

PROF. J. ALBERTUS MYBURGH (Johannesburg, South Africa): Dr. Pitt's results are excellent. I rise mainly to discuss an aspect which has, as he has indicated, been somewhat controversial, namely the necessity for postoperative stenting. At the same time I wish to pay homage to the so-called "French Connection," as Dr. Hepp called it in what, I think, was his first paper on the subject in English. My attention to the Hepp–Couinaud approach was first drawn by Professor Maurice Mercadier when he visited us 12 years ago. I had been unaware of Hepp's and Couinaud's work that appeared in *La Presse Medicale* in 1956. I consulted it immediately, and I have used the method ever since. The essence of this contribution is the ready accessibility of the left hepatic duct, about 1.5 cm of the right hepatic duct, and their confluence, by dissection of the hilar plaque between the caudate and quadrate lobes (segments I and IV).

This has really revolutionized the approach to high bile duct strictures. It allows the performance of a wide −2.5 to 3 cm accurate mucosa-to-mucosa, watertight anastomosis to a Roux loop of jejunum. The slide shows the preliminary placement of a row of sutures into the upper margin of the opened left hepatic duct. This is an essential step. Sutures are then preplaced between the lower margin of the left duct and the corresponding margin of the Roux-loop. The Roux loop is then "parachuted" down and the sutures are tied. The upper layers of sutures are then passed through the corresponding margin of the Roux loop, tied, and the side-to-side anastomosis is complete. I have used this approach consistently, not only in postcholecystectomy strictures but also in primary sclerosing cholangitis, as demonstrated in the slide. (Slide) Here are the results obtained in a personal series of 22 postcholecystectomy strictures followed for 11 years, with a median of 5 years. One half of the patients had had previous attempts at repair elsewhere. Reoperation has been necessary in only one patient. This patient was the last standard end-to-side hepaticojejunostomy I performed before adopting the Hepp approach. No patient has required reintervention after a Hepp procedure. Current serum bilirubin is normal in all patients and serum alkaline phosphatase is also normal in the majority. There have been no episodes of cholangitis after the Hepp procedure.

Similarly in 14 patients with primary sclerosing cholangitis and dominant strictures at the hepatic duct confluence, followed for up to 7 years (median 2.7 years), no patient has required reoperation. Serum bilirubin is normal in all 14 patients, but not surprisingly the serum alkaline phosphatase is raised in 13 in view of the concomitant intrahepatic strictures that are part and parcel of the pathology in most patients.

In none of these postcholecystectomy or primary sclerosing cholangitis patients were any transanastomotic stents used. The Hepp–Couinaud approach provides a safe, durable, and highly effective solution to a problem that has enjoyed considerable notoriety.

It provides a means of achieving an accurate, watertight mucosa-to-mucosa anastomosis without the need for stenting, provided that the principles and details of the procedure are meticulously carried out.

DR. HENRY A. PITT (Closing discussion): Dr. Longmire reminded us that in the past surgical dilatation did not work, and he questioned why balloon dilatation works in some patients. He pointed out that the use of repeated dilatation and prolonged stenting may be the difference. We would agree with that interpretation. In several of our patients, we have been able to dilate the strictures with large balloons and stent for prolonged periods with 18 or 22 French stents.

Dr. Hermann mentioned that at the Cleveland Clinic their long-term results with balloon dilatation suggest only a 50% success rate. Thus their observations confirm our findings. He also asked about complications and, in particular, hemobilia. In our analysis patients managed with balloon dilatation were significantly more likely than surgical patients to develop hemobilia requiring transfusion. Most of the balloon dilated patients with hemobilia had been stented for prolonged periods because of recurrent stricture and had undergone repeated dilatations. These patients, in whom stents have been left for very prolonged periods, may actually be at greater risk for hemobilia.

Both Drs. Hermann and Jones asked what were the indications for balloon dilatation. One group of patients in whom balloon dilatation might be indicated are those at very high risk for anesthesia because of severe cardiac, pulmonary, renal, or liver disease. However advanced age, *per se*, should not be an indication for balloon dilatation. Morbidly obese patients and those who are unwilling to undergo further surgery may also be candidates for balloon dilatation. However these patients should be told that even after several dilatations and 1 year of stenting, surgery may still be necessary. Moreover the overall time and cost of balloon dilatation does not differ from surgery. However if balloon dilatation fails, as it often does, the time to an eventual good outcome will be prolonged when compared to a successful operation.

Dr. Jones also asked about the very high strictures. Among our patients with the Bismuth type IV strictures involving the intrahepatic ducts, we found no differences in outcome between surgery and balloon dilatation.

Professor Myburgh discussed the use of stents. At least four different techniques can be used: (1) no stents, as he suggested; (2) short-term stents; (3) long-term stents, as we have used; and (4) the mucosal graft technique. In reviewing the literature I have been impressed that the results may be correlated more with the length of follow-up than with the type of stenting that has been employed.

We would agree with Professor Myburgh that in certain patients in whom a nice mucosa-to-mucosa anastomosis can be performed that stents may not be necessary. The Bismuth type I patients with more than 2 cm of common hepatic duct had a 100% success rate in this series. That subgroup may not need to be stented. However I was impressed in reviewing the UCLA series, in which we compared the length of stenting and the type of stents, as well as the present and other series, in which long-term transhepatic stents have been used, that the results with this technique have been among the best reported. For this reason we will continue to use long-term transhepatic stents.

Acquired Immune Deficiency Syndrome (AIDS)

Indications for Abdominal Surgery, Pathology, and Outcome

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Thirty-six major abdominal operations were performed on 35 Acquired Immune Deficiency Syndrome (AIDS) patients (33 men, two women). Twenty-two elective operations were indicated for diagnosis of abdominal or retroperitoneal mass (6), incomplete bowel obstruction (5), intra-abdominal infection (4), biliary symptoms (3), thrombocytopenia (3), and toxic megacolon (1). Fourteen emergency operations were for perforated viscus or peritonitis (11), massive gastrointestinal bleeding (2), and cecal volvulus (1). In 5 of 22 (23%) elective operations AIDS was unknown to the treating physicians until diagnosed by the surgical pathology; in contrast, all 14 emergency operations were in patients who had a known diagnosis of AIDS. The operative findings were related to AIDS in 34 of 36 (94%) operations. Cytomegalovirus was the most common pathogen, isolated or identified microscopically in 11 patients (eight emergency and three elective operations). Mycobacterial infections presented as retroperitoneal adenopathy or splenic abscess in six patients. Non-Hodgkins lymphoma was the most common malignancy found, presenting as an abdominal mass (4), bowel obstruction (3), or with gastrointestinal bleeding (2). Kaposi's sarcoma was diagnosed at laparotomy in four patients. The 1-month operative mortality rate for elective operation was 9% (2 of 22) and 46% (6 of 13) in emergencies. Postoperative complications included 1 reoperation for sepsis caused by inadequately resected CMV colitis; 1 pancreatic fistula; 1 wound dehiscence, and 2 minor wound infections.

BY THE END OF THIS DECADE, 100,000 Americans will have AIDS and another 1.5 million will be less symptomatically infected with the HIV-1 retrovirus. Surgeons are now involved in the care of the few AIDS patients who develop acute abdominal symptoms but in the near future are likely to treat electively the greater number of patients with intra-abdominal neoplasms and opportunistic infections secondary to a deficient immune system. In the 8 years since the first description of AIDS, a distinct pattern of HIV-associated surgical disease has emerged. We describe the clinical presentation, indications for operation, short-term outcome, and categorize the surgical pathology encountered in AIDS patients who had abdominal surgery, usually for conditions directly related to AIDS. In most patients the diagnosis of AIDS was known before onset of the complication requiring operation, but in others the surgeon was first to establish the diagnosis by operation.

Patients and Methods

The discharge diagnoses, pathology records, and operating room logs of eight Southern California hospitals from 1984 until 1988 were reviewed to find patients who had a clinical diagnosis of AIDS and had undergone celiotomy. The medical centers included 2 community hospitals, 2 university institutions, 2 Veterans Administration hospitals, 1 health maintenance organization, and 1 urban public hospital. All patients had the clinical manifestations of AIDS conforming with the 1987 revised Centers for Disease Control guidelines[1] before operation, or the diagnosis of AIDS was established by the findings at operation. Serologic confirmation was obtained by both ELISA and Western Blot tests. Patients with HIV infection alone or AIDS-related complex are not included in this report. The medical record was abstracted to obtain the patient's age, sex, indication for operation, gross intraoperative and histologic pathology, complications of operation, and short-term outcome. A detailed case history was prepared for each patient by the attending surgeon. Confidentiality was maintained by omitting patient identification from abstracted material.

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TABLE 1. *Clinical Data on 12 Aids Patients Undergoing Elective Abdominal Operations—Diagnosis of Aids Known Before Surgery*

Age	Sex	Operative Indication	Findings	Surgical Procedure	Survival More than 1 Month
40	M	Cholelithiasis, salmonella sepsis	CMV* in Gallbladder	Cholecystectomy	Yes
31	M	Thrombocytopenia	Splenic congestion; KS† in para-aortic lymph nodes	Splenectomy; lymph node biopsy	No
36	M	Abdominal lymphadenopathy	MAI‡ in mesenteric lymph nodes	Ex. lap., lymph node biopsy	Yes
42	M	Partial bowel obstruction	Lymphoma of cecum	Right hemicolectomy	Yes
34	M	Abdominal lymphadenopathy	Nondiagnostic	Ex. lap., lymph node biopsy	Yes
26	F	Acalculous cholecystitis	Candida in gallbladder	Cholecystectomy	Yes
39	M	Partial bowel obstruction	KS in colon, rectum	Diverting colostomy	Yes
40	M	Small bowel obstruction	Adhesions	Ex. lap., lysis of adhesions	Yes
30	M	Chronic RLQ pain	CMV in appendix	Appendectomy	Yes
35	M	Splenic abscesses	MAI abscesses of spleen	Splenectomy	Yes
30	M	Splenic abscess	M. tuberculosis of spleen	Splenectomy	Yes
32	M	Thrombocytopenia	Noncaseating granuloma	Splenectomy	Yes

* CMV, Cytomegalovirus.
†KS, Kaposi's Sarcoma.
‡MAI, Mycobacterium avium-intracellulare.

Results

Thirty-five patients with clinically diagnosed AIDS had 36 operations. The average age of the patients was 38.7 years (range, 26 to 59 years); 33 patients were men and two were women. Twenty-two operations were elective and 14 were emergent. Twelve of the 22 patients undergoing elective operation had an established diagnosis of AIDS before surgery (Table 1). Among the ten patients not previously known to have AIDS, the clinical presentation suggested AIDS in five and these patients were seropositive for Human Immunodeficiency Virus (HIV) infection on preoperative testing (Table 2). Neither seropositivity for HIV infection nor presence of AIDS was apparent before operation in five of the 33 (15%) and the diagnosis was only recognized by the surgical findings or soon thereafter on histopathologic grounds. All of the patients who required emergency operation were known to have AIDS (Table 3).

Clinical Presentation

Emergency operations were required for treatment of peritonitis (11 patients), and gastrointestinal hemorrhage (2 patients), or cecal volvulus (1 patient). Cytomegalovirus (CMV) infection of the small or large bowel with perforation was the reason for eight of 11 explorations for peritonitis. CMV infection and perforations were typically found at multiple sites in the jejunum, ileum, and colon. Surgical management was either resection of all involved bowel, oversewing of perforations, or a combination of both. Three operations were for peritonitis not caused by CMV. A 31-year-old man who had received 2000 rads of radiation therapy for a large undifferentiated lymphoma of the duodenum developed generalized peritonitis. Duodenal perforation caused by tumor necrosis was treated by partial duodenectomy with anastomoses at the ampullary level. Necrosis of a non-Hodgkins lymphoma caused perforation of the terminal ileum in a 39-year-old man. A 32-year-old man developed peritonitis after a CT-guided needle aspirate of retroperitoneal lymph nodes. No bowel perforation was identified at laparotomy but cultures and lymph node biopsy demonstrated *Mycobacterium avium-intracellulare* (MAI).

Massive gastrointestinal hemorrhage was the indication for emergency operation in two patients. A 37-year-old man received chemotherapy for a small cell lymphoma of the stomach and 3 weeks later hematemesis and hypotension necessitated a subtotal gastrectomy (Table 4). A 42-year-old man had profuse lower gastrointestinal tract bleeding and at laparotomy was found to have extensive lymphadenopathy adjacent to the small bowel. No bowel was resected, but lymph node and small bowel biopsies were taken, showing CMV infection and diffuse large cell lymphoma.

A 44-year-old man who had abdominal pain and radiographic studies suggesting bowel obstruction and vol-

TABLE 2. *Clinical Data on 10 Aids Patients Undergoing Elective Abdominal Operations—Diagnosis of Aids Not Established Before Surgery*

Age	Sex	AIDS Dx. Suspected?	Operative Indication	Findings	Surgical Procedure	Survival More than 1 Month
38	M	No	Toxic megacolon	CMV* colitis	Colon resection	Yes
59	M	No	Cholelithiasis choledocholithiasis	KS† in cystic duct	Cholecystectomy, CBDE	Yes
51	M	No	Thrombocytopenia	Splenomegaly, lymphoid hyperplasia	Splenectomy	Yes
29	M	Yes, HIV(+)	Partial bowel obstruction, mass	Lymphoma of terminal ileum with pelvic extension	Bypass of involved bowel, colostomy	Yes
53	M	No	Gastric mass, bleeding	Gastric lymphoma	Gastric resection	Yes
34	M	Yes, HIV(+)	Painful LUQ mass	Lymphoma of spleen	Splenectomy	Yes
59	M	Yes, HIV(+)	Partial bowel obstruction	Lymphoma of terminal ileum with intussusception	Bowel resection	Yes
34	F	No	Malabsorption	Nondiagnostic	Ex. lap., jejunal and lymph node biopsies	Yes
39	M	Yes, HIV(+)	Abdominal lymphadenopathy	MAI‡ in lymph nodes	Ex. lap., lymph node biopsies	Yes
34	M	Yes, HIV(+)	Abdominal lymphadenopathy	KS, MAI in lymph nodes	Ex. lap., lymph node biopsies	No

* CMV, Cytomegalovirus.
† KS, Kaposi's Sarcoma.
‡ MAI, Mycobacterium avium-intracellulare.

TABLE 3. *Clinical Data on 13 Aids Patients Undergoing Emergency Abdominal Operation*

Age	Sex	AIDS Dx. Known	Operative Indication	Findings	Surgical Procedure	Survival More than 1 Month
37	M	Yes	Peritonitis	CMV* colitis—perforated	Colon resection	Yes
31	M	Yes	Peritonitis	Lymphoma of duodenum—perforated	Duodenectomy	No
37	M	Yes	Massive UGI hemorrhage	Bleeding gastric lymphoma	Gastric resection	Yes
32	M	Yes	Peritonitis after CT-guided biopsy	MAI† adenopathy	Exploration, lymph node biopsy	Yes
44	M	Yes	Peritonitis	CMV of jejunum—perforated	Small bowel resection	Yes
27	M	Yes	Peritonitis	CMV of transverse colon, perforated	Colon resection	Yes
40	M	Yes	Peritonitis	CMV of ileum, perforated	Oversewing of perforations	No
57	M	Yes	1) Peritonitis 2) Peritonitis (one week postop.)	1) CMV colitis, perforated cecum and sigmoid colon 2) Perforated sigmoid colon	1) Resection of right colon oversewn sigmoid colon 2) Sigmoid colectomy	No
27	M	Yes	Peritonitis	CMV colitis—perforated	Colon resection	No
42	M	Yes	Massive GI bleeding	CMV and lymphoma	Colon resection	No
44	M	Yes	Cecal volvulus	Cecal volvulus	Right hemicolectomy	No
52	M	Yes	Pneumoperitoneum	CMV of jejunum, perforated	Small bowel resection	Yes
39	M	Yes	Peritonitis	Perforation non-Hodgkins lymphoma ileum	Ileocolonic resection	Yes

* CMV, Cytomegalovirus.
† MAI, Mycobacterium avium-intracellulare.

TABLE 4. *Postoperative Complications in 33 Aids Patients Who Had Abdominal Surgery*

Age	Sex	Operation	Complication	Survival More than 1 Month
27	M	Colon resection for CMV* perforation	Wound dehiscence, postoperative day 9	No
57	M	Colon resection for CMV perforation	Sigmoid leak and peritonitis, postoperative day 8	No
39	M	Exploratory laparotomy with lymph node biopsies	Superficial wound infection, postoperative day 11	Yes
37	M	Hemigastrectomy for bleeding gastric lymphoma	Pancreatic fistula, postoperative day 15	Yes
32	M	Splenectomy	Superficial wound infection, postoperative day 10	Yes

* CMV, Cytomegalovirus.

vulus was found to have a cecal volvulus. This was one of the two pathologic findings unrelated to AIDS.

Elective operations were for specific therapeutic indications in 15 of the 22 patients and for diagnosis only in the other five patients. Five splenectomies were done for thrombocytopenia,[2] immunoblastic sarcoma, (B-cell type malignant lymphoma), and *Mycobacterium avium-intracellulare* and *Myobacterium tuberculosis* splenic abscesses.

Three cholecystectomies were performed: 1 for cholelithiasis and resistant salmonella sepsis (CMV was present in gallbladder mucosa), 1 for acalculus cholecystitis caused by candida, and 1 for biliary symptoms in a 59-year-old who did not have preoperative diagnosis of AIDS but was found to have Kaposi's sarcoma of the cystic duct.

Symptoms of partial or intermittent bowel obstruction led to exploration in five patients, one of whom had a palpable right lower quadrant abdominal mass. Non-Hodgkins lymphoma was the cause of the obstruction in three, with the tumor located in the terminal ileum in two and in the cecum in the third patient. Bowel obstruction was caused by the lymphoma acting as the intussusceptum for an intussusception at the ileocecal valve in another. Kaposi's sarcoma caused near-total obstruction of the rectum in a 39-year-old man who was palliated with diverting sigmoid colostomy. A small bowel obstruction was caused by adhesions in a 40-year-old man who was one of only two patients to have no AIDS-related pathology at surgery.

Six abdominal explorations were performed for diagnosis because of unexplained abdominal or retroperitoneal lymphadeonpathy in patients suspected of having opportunistic infection. *Mycobacterium avium-intracellulare* was isolated from excised lymph nodes in two of these patients, both Kaposi's sarcoma and MAI in another, and the fourth patient was nondiagnostic. Jejunal and lymph node biopsies were nondiagnostic in a 34-year-old woman with severe malabsorption, but she was later found to have *Strongyloides* infection. A 30-year-old man who had AIDS diagnosed 2 years before developed persistent abdominal pain. Exploration uncovered a chronic appendiceal abscess secondary to CMV infection of the appendix.

The presentations of the five patients with undiagnosed AIDS varied. Two examples illustrate this problem. A 53-year-old apparently healthy man, evaluated for guaiac-positive stools by upper gastrointestinal endoscopy, had an invasive gastric neoplasm, interpreted as adenocarcinoma on biopsy. After subtotal gastric resection, pathology demonstrated a non-Hodgkins lymphoma, large cell type, and the patient's HIV tests were seropositive, confirming the diagnosis of AIDS. A 38-year-old year old man who was diagnosed before operation to have a toxic megacolon syndrome, believed due to ulcerative colitis, was found instead to have cytomegalovirus enterocolitis with dilated, nonperforated bowel.

Morbidity and Mortality

Only 2 of the 22 patients (9%) undergoing elective surgery died within the first 30 postoperative days, in contrast to the 6 of 11 patients (46%) who died after emergency exploration. Deaths were caused by progression of AIDS and a combination of sepsis, particularly *Pneumocystis carinii* pneumonia and bacteremia.

Surgical complications developed postoperatively in five patients (Table 4). The fascia of a midline abdominal wound separated in a 27-year-old man who had a colon resection for CMV gastroenteritis with perforation of the transverse colon and diffusing peritonitis. The dehiscence was managed nonoperatively because of severe *Pneumocystis* pneumonia and he died of respiratory failure four days later. A 57-year-old man who had cecal and sigmoid colon perforations developed an intra-abdominal perforation proximal to the site of an exteriorized repair of the sigmoid colon. He survived only 1 week after reoperation for subtotal colonic resection. A 37-year-old man who had massive hematemesis from gastric lymphoma treated by hemigastrectomy developed a pancreatic fistula *via* a Jackson-Pratt drain 15 days after operation. He died 1 month later. The other surgical com-

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plications were two superficial wound infections that resolved with routine dressing changes.

Intercurrent medical complications related to AIDS were common in the emergency surgery group, and included *Pneumocystis pneumonia* and bacterial sepsis.

Discussion

Abdominal surgery is unusual in patients with AIDS. In 4 years only 35 patients were collected from eight hospitals (3500 beds) in Southern California. In the endemic New York area just ten emergency abdominal operations were performed in AIDS patients in 3 years at one university and two municipal hospitals.[3] Only 5 of 110 (4.5%) AIDS patients reported by Nugent and O'Connell[2] in Los Angeles underwent therapeutic operations, and similarly, 36 of 904 (4.2%) AIDS patients treated by LaRaja et al.[4] in New York. Abdominal symptoms, however, are common in AIDS patients, but surgical illness is not the cause in most. The general surgeon will be consulted for evaluation of suspected peritonitis. Of 235 AIDS patients reviewed by Barone et al.,[5] 29 had abdominal pain but only five (2.1%) underwent exploration. The etiology of the abdominal pain is often an infectious gastroenteritis, and treatment with specific antimicrobial agents and observation to detect peritonitis from perforation is a cautious recommendation.

In most patients the diagnosis of AIDS will be known to the surgeon before operation and in a few elective operations, the operative findings establish the diagnosis.

Four clinical syndromes are apparent from analysis of our patients: (1) peritonitis secondary to CMV enterocolitis and perforation; (2) non-Hodgkins lymphoma of the gastrointestinal tract, usually the terminal ileum, presenting as obstruction or bleeding; (3) Kaposi's sarcoma of the gastrointestinal tract; and (4) mycobacterial infection of the retroperitoneum or spleen.

The cytomegalovirus, one of the five members of the herpes virus family, causes clinically significant infection in more than 50% of AIDS patients. *Candida* and *Pneumocystis carinii* are more frequent opportunistic infections, but unlike these pathogens, CMV infects the endothelial cells of capillaries in the gut mucosa leading to a diffuse, ulcerative gastroenteritis. CMV colitis may be recognized by endoscopic visualization of the multiple, well-circumscribed ulcerations that have an overlying fibrinous exudate.[6] Biopsy reveals characteristic CMV inclusions in endothelial cells. The vasculitis of the mucosal and submucosal capillary beds in the gut may lead to necrosis and perforation. This was the principal indication for emergency operation for peritonitis in our patients. Resection of all grossly diseased bowel and diversion by ileostomy or colostomy is advisable to avoid anastomotic breakdown. Outcome is poor for CMV perforation, with only three of eight patients surviving 1 month after operation. The single abdominal fascial disruption occurred in a patient who had inadequate resection of a CMV colonic perforation without exteriorization. Spontaneous peritonitis may be caused by other opportunistic pathogens, including *Mycobacterium avium-intracellulare, Myobacterium tuberculosis, Cryptococcus neoformans,* and *Strongyloides.*[7,8]

Malignant lymphoma is known to occur when the immune function is depressed, as in AIDS and immunosuppressed renal transplant patients. The AIDS-associated lymphomas are high-grade malignancies of B-lymphoid lineage and include immunoblastic lymphoma and small, noncleaved lymphoma, although large, noncleaved cell and intermediate cell lymphomas have also been described. B-cell lymphomas are believed to be caused by repression of T-4 lymphocytes and reversal of the T4:T8 (helper:suppressor) ratio to 0.5 or less. The T4 lymphocytopenia allows spontaneous B-cell hyperactivity. The significantly increased incidence of non-Hodgkins lymphoma in patients with HIV infection led to a revision of the case definition for AIDS by the Center for Disease Control in June 1985, to include high-grade, B-cell lymphomas in patients with positive serology (presence of antibody) or virology (positive viral culture) for HIV.

The current incidence of HIV infection should indicate to the surgeon that the first manifestation of AIDS may be obstruction or bleeding caused by a non-Hodgkins B-cell lymphoma in any segment of the gastrointestinal tract, but particularly the distal ileum. The indication for operation may be a palpable mass, bowel obstruction, or gastrointestinal bleeding. Perforation of tumor appears to follow radiotherapy and chemotherapy. The operative strategy should be to remove the tumor and, if not possible, restore intestinal function by enterocolostomy or enteroenterostomy. The short-term outlook for these patients justifies operation because six of the seven patients were alive from 1 month to 1 year.

The violaceous macules of Kaposi's sarcoma, a multifocal neoplasm of the reticuloendothelial system, are visible on upper and lower endoscopy in approximately 40% of AIDS patients but cause few surgical complications.[9] Only two of our patients had operation for gastrointestinal tract symptoms due to Kaposi's sarcoma. Manifestations are likely to be obstruction or rectal ulcerations, and many sites, including the biliary tree or lymph nodes, may be involved. Gastrointestinal Kaposi's sarcoma has a poor prognosis.

Splenectomy in AIDS for thrombocytopenia refractory to medical treatment has been previously reported,[10] and was done in three of our patients. Correction of immunodeficiency-associated thrombocytopenic purpura by splenectomy can be anticipated in 60% to 70% of patients.[11] Splenectomy was also required for splenic infection (mycobacterial abscess) or neoplasm (immunoblastic lymphoma). If enlarged retroperitoneal lymph nodes are suspected to have MAI infection, we recommend obtaining diagnosis by blood culture, bone marrow biopsy, or superficial node biopsy rather than operation.

Gloomy predictions of "great difficulty in successfully operating on patients with AIDS" is not borne out in this analysis of elective operations. Poor wound healing was not a serious hazard and mortality was low. On the other hand, few patients survive emergency operation for peritonitis, postoperative systemic infection is common, and progression of AIDS is rapid. The surgeon must recognize the disease syndromes associated with AIDS before operation and confirm HIV infection with serology tests in patients with typical presentations and risk factors.

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DISCUSSION

DR. WILLIAM M. STAHL (Bronx, New York): I appreciate the data that Dr. Robinson, Dr. Miller, and Dr. Wilson have given us on the AIDS problem, which is more important for us in some parts of the country than in others.

Our experience has been the same in that the AIDS-related problems requiring surgery have been very low, as reported by Dr. Laraja from our medical school.

I would like to address just briefly the question of the undiagnosed patient who is coming to operation for a variety of reasons, in our case, major trauma.

There are three scourges in the inner city at the moment. They are drugs, handguns, and AIDS, all obviously interrelated. We are responsible in the South Bronx for about 500,000 people. We have about 60% intravenous drug-associated admissions. The handgun gives us 1000 penetrating wounds per year. At last count 1 month ago, of our 6000-plus deliveries, 1 of every 57 babies is HIV positive.

In the course of a study last year of admissions on major trauma patients with more than 20 ISS, we looked at the first 19 and my immunobiologist said, "Some of these patients are clearly abnormal. What is going on?" We went back and evaluated them and 3 of the 19 were HIV positive. The first thing we learned was that in some parts of the country, 15% to 20% of admissions may be unsuspectedly HIV positive. These patients had no clinical indications that they were any different than anyone else. They all had survived their injuries and went home.

(Slide) I would like to show very briefly three slides that will show what their immunologic profiles were. I believe that these are not known. The first slide shows the CD-3 lymphocytes, the pan T cells in those patients, the normals being the dashed line and the abnormals the straight line. This shows that all their T cells go down as usual after major injury, but then tend to come up by 7 days. They are no different in terms of pan T cells. (Slide) But they do not have any C-4 cells. We assume that the developing protein of the HIV binds to the C-4 receptor and kills the cells apparently early on. The normals being depressed increase again as we expect, but the abnormals have no helper cells at all for all practical purposes, and of course, their CD-4/8 ratios are totally different.

I think this tells us something. One is that these patients are clinically indistinguishable from normal patients, and we must be careful because they are in high numbers in certain parts of the country. The normal infectious processes that we see in post-trauma patients do not seem to occur in these patients, in spite of the fact that they are clearly immunologically abnormal. It prompts the question of what does the helper cell do in these patients who survive without having these cells around.

DR. THOMAS C. MOORE (Torrance, California): Dr. Wilson's excellent report from one of the centers and points of origin in this country of the AIDS epidemic/pandemic is most timely and brings this disorder to the diagnostic and therapeutic attention of surgeons. As a highly lethal disease with no effective treatment, AIDS is both a challenge and a hazard to the surgeon. The development of AZT-resistant AIDS virus strains only enhances the uniformly bad news up to this point.

As our distinguished basic science lecturer, Dr. Gallo, has pointed out, the HIV(AIDS) virus is targeted to CD4 cell surface molecules on T lymphocytes, macrophages, and brain cells. There is mounting evidence that the virus envelope, particularly the external envelope gp120, and its excessive production and shedding may play an important role in the cytopathic effects of HIV infection and the development of symptomatic AIDS. It has been suggested that vasoactive intestinal peptide (VIP) may be the endogenous substance whose receptor is used by the HIV(AIDS) virus gp120 for intracellular access.

We at the Harbor-UCLA Medical Center have been interested in the *in vivo* effects of core pentapeptides from both VIP (vasoactive intestinal peptide) and the HIV(AIDS) gp120 on lymphocyte traffic in sheep. These core pentapeptides are highly conserved and biologically active both *in vitro* and *in vivo* and differ by only one amino acid. They are TTNYT for the HIV(AIDS) virus gp120 and TDNYT for vasoactive intestinal peptide. The TDNYT represents residues 7 through 11 of the 28 amino acid residue VIP molecule.

The first slide shows the prompt, prolonged, and markedly depressant effects of both the HIV gp120 TTNYT pentapeptide and the whole 28 amino acid residue VIP molecule on lymphocyte traffic through primary peripheral (popliteal) lymph nodes of sheep *in vivo* after acute infusion into chronically cannulated nodal afferent lymphatics. The output of both small recirculating and blast lymphocytes into study node efferent lymph was affected and with a selective effect on T-4 (CD4) lymphocytes. The results were similar, as this slide shows. Similar results also were obtained with acute infusions of the TDNYT core pentapeptide molecule of VIP, as shown in this slide. From previous and related studies, these findings were interpreted as immunosuppressive. The traffic of lymphocytes through lymphoid tissues and lymph nodes is of major importance in the initiation and development of the immune response. Details of these studies have been published in two papers in the last 8 months: Moore TC, Spruck CH, and Said SI: Depression of Lymphocyte Traffic in Sheep by Vasoactive Intestinal Peptide (VIP). Immunology 1988; 64: 475, and Moore TC, Spruck CH, and Said SI: *In Vivo* Depression of Lymphocyte Traffic in Sheep by VIP and HIV(AIDS) Related Peptides. Immunopharmacology 1988; 16:181.

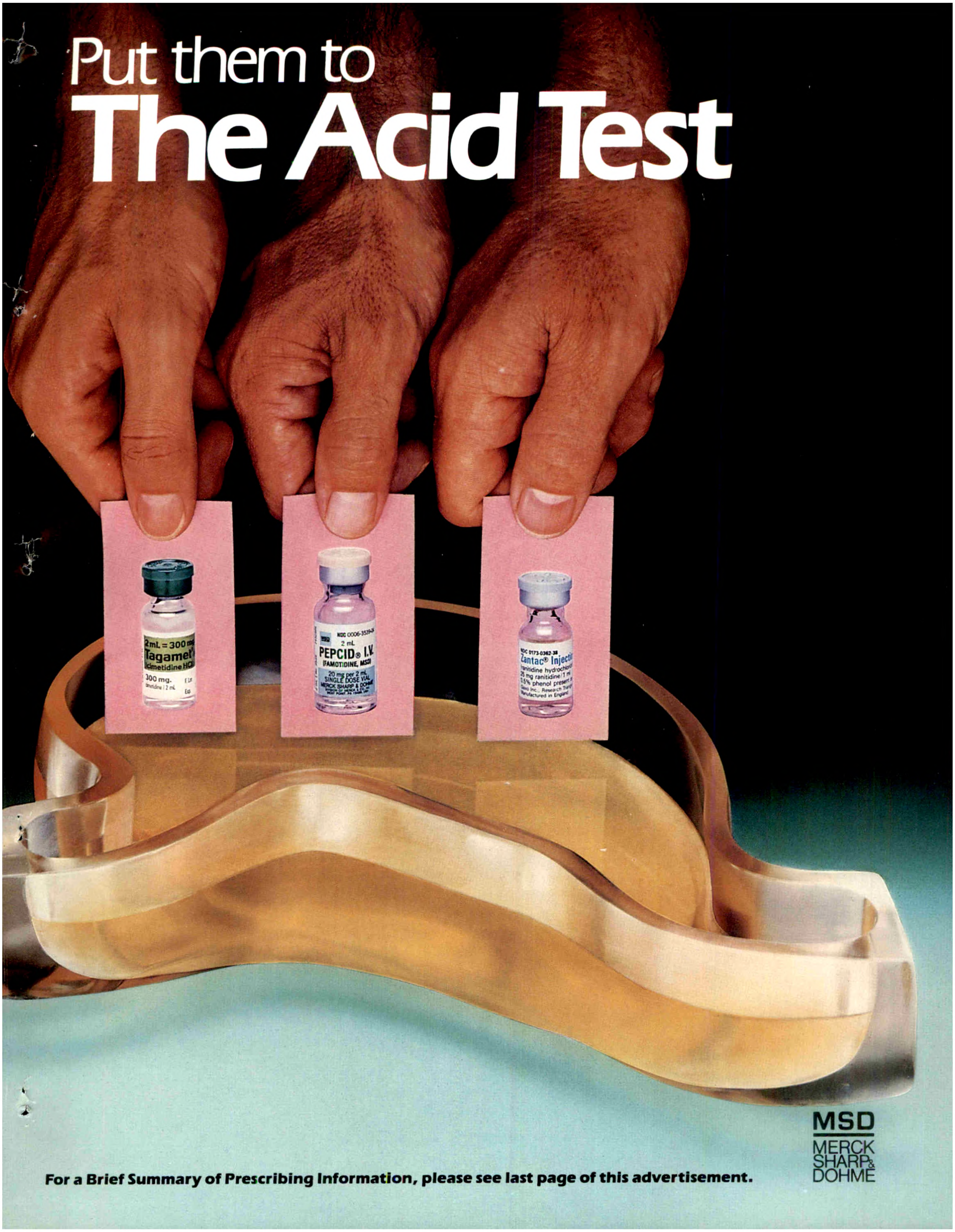
A reverse and stimulant effect on lymphocyte traffic has been observed after acute afferent lymphatic infusions of substance P and of bradykinin. This slide shows a marked, profound, and prolonged stimulatory effect of substance P on T4 (CD4) lymphocyte traffic and output into efferent lymph—a stimulant effect lasting through the 96 hours of monitoring after a single afferent lymphatic infusion of only 50μg of substance P. The marked and prolonged substance P enhanced output of T4 (CD4) lymphocytes from lymph nodes and the associated depression in the output of T8 (CD8) and B lymphocytes is the reversal of the findings in HIV(AIDS) infection in humans, in whom there is a decrease in the T4: T8 lymphocyte ratios and an increase in B cells from polyclonal B cells proliferation. This observation and this molecule may have some therapeutic potential with respect to the clinical management of HIV(AIDS) infection in humans.

DR. THOMAS K. HUNT (San Francisco, California): There are two important biologic points brought out by this paper and Dr. Gallo's talk. The AIDS virus, as Dr. Gallo noted, kills T cells and affects, but does not kill, macrophages. There have been about half a dozen papers on results of surgery in AIDS victims. Neither wound healing nor wound infection, in general, have been problems. This demonstrates the relative lack of importance of T cells in healing and wound infection. The reason I make that point is that much of the research on immune mechanisms in wound infection is targeted at specific immune mechanisms, which are probably not very relevant, and with regard to these points I would like to ask, can Dr. Wilson tell us the bacteriology of his two wound infections?

DR. SAMUEL E. WILSON (Closing discussion): Dr. Stahl, thank you for sharing your experience from a large urban, public hospital. I would point out that there is a somewhat different epidemiology in Southern California than in New York, and that the patients we presented here represent a broad cross section of university and community hospitals from Los Angeles to San Diego. None of the institutions surveyed would qualify as an inner-city hospital, so I think we do have to bear in mind that any practicing surgeon may have cause to treat these complications.

Dr. Moore has discussed a possible strategy for therapy and I wish to emphasize that the lack of effective chemotherapy renders surgical treatment of some of these complex infections all the more important, particularly mycobacterium abscesses in the spleen.

Dr. Hunt, both wound infections were gram positive cocci.



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PEPCID® I.V. (Famotidine, MSD) is indicated in some hospitalized patients with pathological hypersecretory conditions or intractable ulcers or as an alternative to the oral dosage forms for short-term use in patients who are unable to take oral medication.

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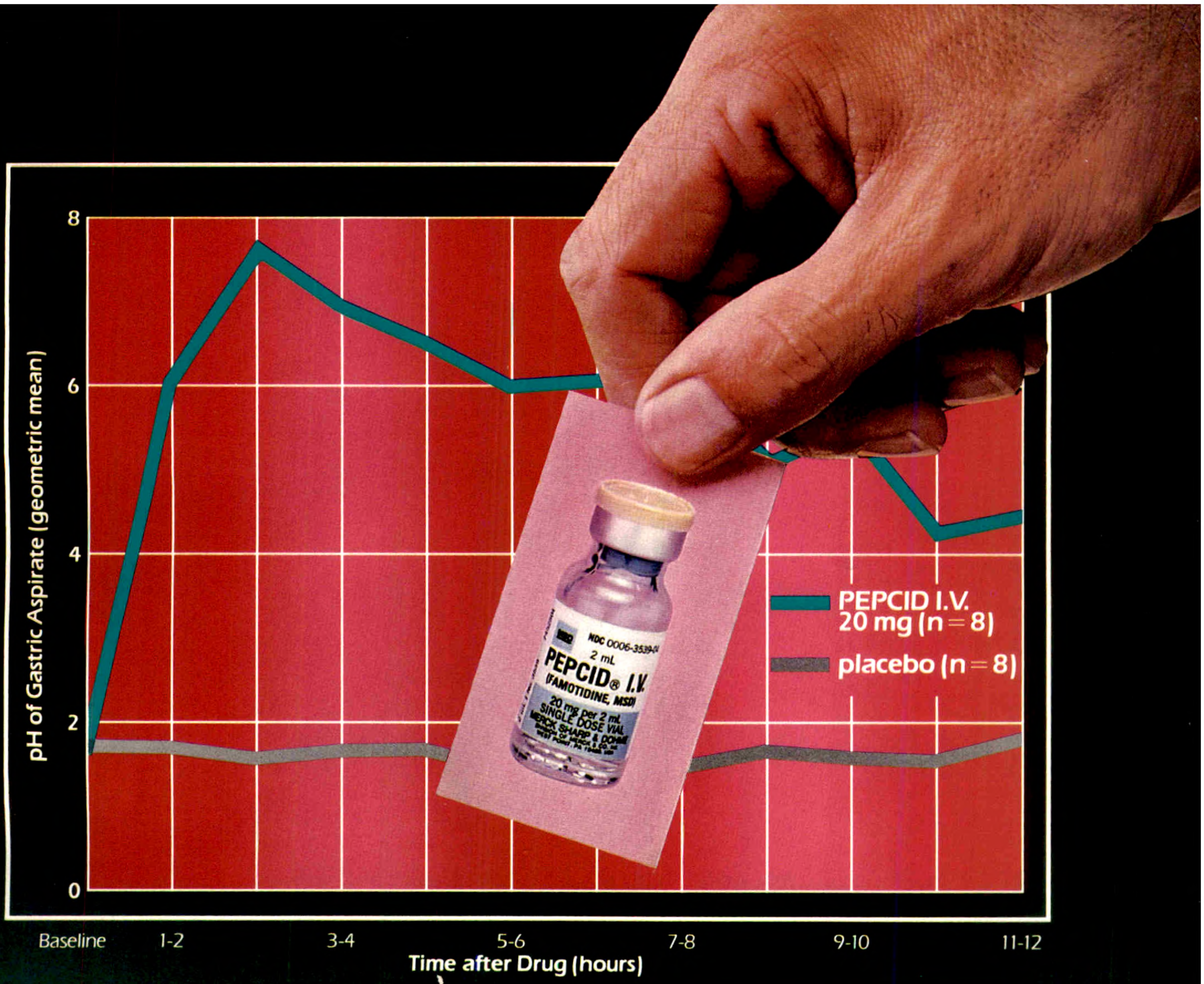

A double-blind, placebo-controlled study[1] involving eight volunteer hypersecretor subjects. The pH of gastric aspirates was measured hourly for 12 hours following single intravenous doses. PEPCID I.V. maintained the mean gastric pH above 4.0 at all time points throughout the 12-hour period with one 20-mg I.V. dose.

[1] Ryan, J.R. et al.: Comparison of effects of oral and intravenous famotidine on inhibition of nocturnal gastric acid secretion, Am. J. Med. 81 (Suppl. 4B): 60-64, October 24, 1986.

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Information for Patients: The oral suspension should be shaken vigorously for 5 to 10 seconds prior to each use, and unused constituted oral suspension should be discarded after 30 days.

Drug Interactions: No drug interactions have been identified. Compounds tested in man include warfarin, theophylline, phenytoin, diazepam, aminopyrine, and antipyrine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In rats and mice given oral doses up to approximately 2,500 times the recommended human dose for active duodenal ulcer, there was no evidence of carcinogenic potential; at these doses in rats, fertility and reproductive performance were not affected. No evidence of a mutagenic effect was observed.

Pregnancy: *Pregnancy Category B*—There are no adequate or well-controlled studies in pregnant women. Use during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether famotidine is secreted into human milk; however, it is secreted into the milk of lactating rats. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: No dosage adjustment is required based on age but may be necessary in severe renal impairment (see Clinical Pharmacology section of Prescribing Information).

Adverse Reactions: The adverse reactions listed below have been reported during domestic and international clinical trials in approximately 2,500 patients. In the placebo-controlled clinical trials, the incidence of adverse experiences with PEPCID Tablets 40 mg at bedtime was similar to that with placebo.

Incidence Greater than 1%: The following adverse reactions have been reported to occur in more than 1% of patients on therapy with PEPCID in controlled clinical trials and may be causally related to the drug: headache (4.7%), dizziness (1.3%), constipation (1.2%), and diarrhea (1.7%).

Causal Relationship Unknown: The following other adverse reactions have been reported infrequently and within each category are listed in order of decreasing severity. The relationship to therapy with PEPCID has been unclear in many cases. *Body as a Whole*—Fever, asthenia, fatigue. *Cardiovascular*—Palpitation. *Gastrointestinal*—Cholestatic jaundice, liver enzyme abnormalities, vomiting, nausea, abdominal discomfort, anorexia, dry mouth. *Hematologic*—Thrombocytopenia. *Hypersensitivity*—Anaphylaxis, angioedema, orbital or facial edema, urticaria, rash, conjunctival injection. *Musculoskeletal*—Musculoskeletal pain, arthralgia. *Nervous System/Psychiatric*—Grand mal seizure; psychic disturbances including depression, anxiety, decreased libido, hallucinations; paresthesia; insomnia; somnolence. *Respiratory*—Bronchospasm. *Skin*—Alopecia, acne, pruritus, dry skin, flushing. *Special Senses*—Tinnitus, taste disorder.

The adverse reactions reported for PEPCID Tablets may also occur with PEPCID Oral Suspension or PEPCID I.V.; in addition, transient irritation at the injection site has been observed with PEPCID I.V.

AV block has been reported with other H_2-receptor antagonists, but not with famotidine.

Management of Overdosage: There is no experience to date with deliberate overdosage. Up to 640 mg/day have been given to patients with pathological hypersecretory conditions with no serious adverse effects. In the event of overdosage, treatment should be symptomatic and supportive. Unabsorbed material should be removed from the gastrointestinal tract, the patient should be monitored, and supportive therapy should be employed.

Dosage and Administration: ***Duodenal Ulcer:*** The recommended adult oral dosage for active duodenal ulcer is 40 mg h.s.; most patients heal within 4 weeks, and it is rarely necessary to use the full dosage for longer than 6 to 8 weeks. A regimen of 20 mg b.i.d. is also effective. For maintenance therapy, the recommended oral dosage is 20 mg h.s.

Benign Gastric Ulcer: The recommended adult oral dosage for active benign gastric ulcer is 40 mg h.s.

Pathological Hypersecretory Conditions (e.g., Zollinger-Ellison Syndrome, Multiple Endocrine Adenomas): The dosage varies with the individual patient; the recommended adult oral starting dosage is 20 mg q6h, but some patients may require a higher starting dosage. Dosages should be adjusted to individual patient needs and continued as long as clinically indicated; up to 160 mg q6h have been administered to some patients with severe Zollinger-Ellison syndrome.

Oral Suspension: The oral suspension may be substituted for tablets.

Directions for Preparing PEPCID Oral Suspension: Prepare suspension at time of dispensing. Slowly add 46 mL Purified Water. Shake vigorously for 5 to 10 seconds immediately after adding the water and immediately before use.

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Concomitant Use of Antacids: Antacids may be given concomitantly if needed.

Dosage Adjustment for Patients with Severe Renal Insufficiency: In patients with severe renal insufficiency (creatinine clearance less than 10 mL/min), the elimination half-life of famotidine may exceed 20 hours, reaching approximately 24 hours in anuric patients. Although no relationship of adverse effects to high plasma levels has been established, to avoid excess accumulation of the drug, the dosage may be reduced to 20 mg h.s. or the dosing interval may be prolonged to 36 to 48 hours as indicated by the patient's clinical response.

How Supplied: Tablets, containing 20 mg or 40 mg famotidine, with hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxides, magnesium stearate, microcrystalline cellulose, starch, talc, and titanium dioxide as inactive ingredients, in unit-of-use bottles of 30 and unit-dose packages of 100; Oral Suspension, containing 40 mg famotidine per 5 mL after constitution with 46 mL Purified Water, with citric acid, flavors, microcrystalline cellulose and carboxymethylcellulose sodium, sucrose, and xanthan gum as inactive ingredients, and sodium benzoate 0.1%, sodium methylparaben 0.1%, and sodium propylparaben 0.02% added as preservatives, in bottles of 400 mg famotidine for constitution; Solution for intravenous injection, containing 10 mg famotidine per mL, with L-aspartic acid 4 mg, mannitol 20 mg, and Water for Injection q.s. 1 mL as inactive ingredients, and benzyl alcohol 0.9% added as preservative to the multidose vial, as 10x2-mL single-dose vials and as 4-mL vials.

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Fifteen-Year Experience with 1678 Hancock Porcine Bioprosthetic Heart Valve Replacements

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The Hancock porcine valve was the first commercially available biologic heart valve and has been in continuous use at the Brigham and Women's Hospital since January 1972. Through December 1987 we implanted 1678 valves in 1533 patients (885 male; 648 female; 17 to 95 years of age, with a mean of 60 years). There were 825 aortic valve replacements (AVR), 562 isolated mitral valve replacements (MVR), and 146 aortic mitral replacements (DVR). Ninety-four per cent of the patients were functional class III or IV. Associated coronary bypass was done in 25% of patients. Four per cent of patients were lost to follow up during a 1- to 16-year period with a mean of 6 years. Morbidity and mortality rates on a actuarial basis were calculated 10 and 15 years after operation for AVR, MVR, and DVR. The data indicates that the probability of reoperation for structural valve failure is quite reasonable as of 10 years, but from 10 to 15 years the numbers sharply fall off so that the probable effective life of the valve is 10 years. However in the elderly age group (equal to or greater than 70 years of age) the incidence of structural valve degeneration is markedly diminished, making this an ideal valve substitute for the elderly. It is also an ideal valve substitute in any patient who has a contraindication to long-term anticoagulation because of current medical or surgical problems.

THE HANCOCK PORCINE BIOPROSTHETIC VALVE, stabilized with Glutaraldehyde (City Chemical, New York, NY), was the first commercially available quality-controlled, biologically derived heart valve used extensively in humans for the treatment of acquired and congenital heart disease (Fig. 1). This device, inserted first in 1970, derived from experimental work by Carpentier et al.,[1] who had shown that porcine valve tissue could be treated with Glutaraldhyde, and demonstrated experimentally and clinically its durability. This work derived from earlier work by Duran and Gunning,[2] who showed that porcine valves could be modeled into usable devices for heart valve replacement. The porcine valve was seen as an alternative to the use of human valve tissue (allografts), which has always been in short supply.[3,4]

In January 1972 the Brigham and Women's Hospital (then the Peter Bent Brigham Hospital) began clinical implantation of the Hancock porcine valve. Since then there have been numerous clinical reports about this valve,[5–7] the most extensively studied heart valve other than the Starr-Edwards ball valve, the first commercially available and quality-controlled heart valve replacement device of any kind.[8]

This report details our experience with 1678 Hancock porcine heart valves inserted in 1533 consecutive patients operated on from January 1972 through December 1987. This long follow-up series allows for conclusions about indications for insertion of this device and its place in the treatment of valvular heart disease.

Materials and Methods

Beginning in January 1972 and concluding on December 31, 1987, this series includes every patient who had a Hancock stabilized Glutaraldehyde porcine bioprosthetic valve inserted during this time period. All demographic data presented is as of the date of implantation of the valve and includes age, sex, functional class, predominant valve hemodynamic lesion, presence or absence of other cardiac conditions, and other cardiac operations (Table 1).

Data retrieval, entry, and analysis were carried out between October and December 1988, providing a follow-up of 1 to 16 years, with a mean of 6 years. Patients not physically seen in the previous 3 months were brought in

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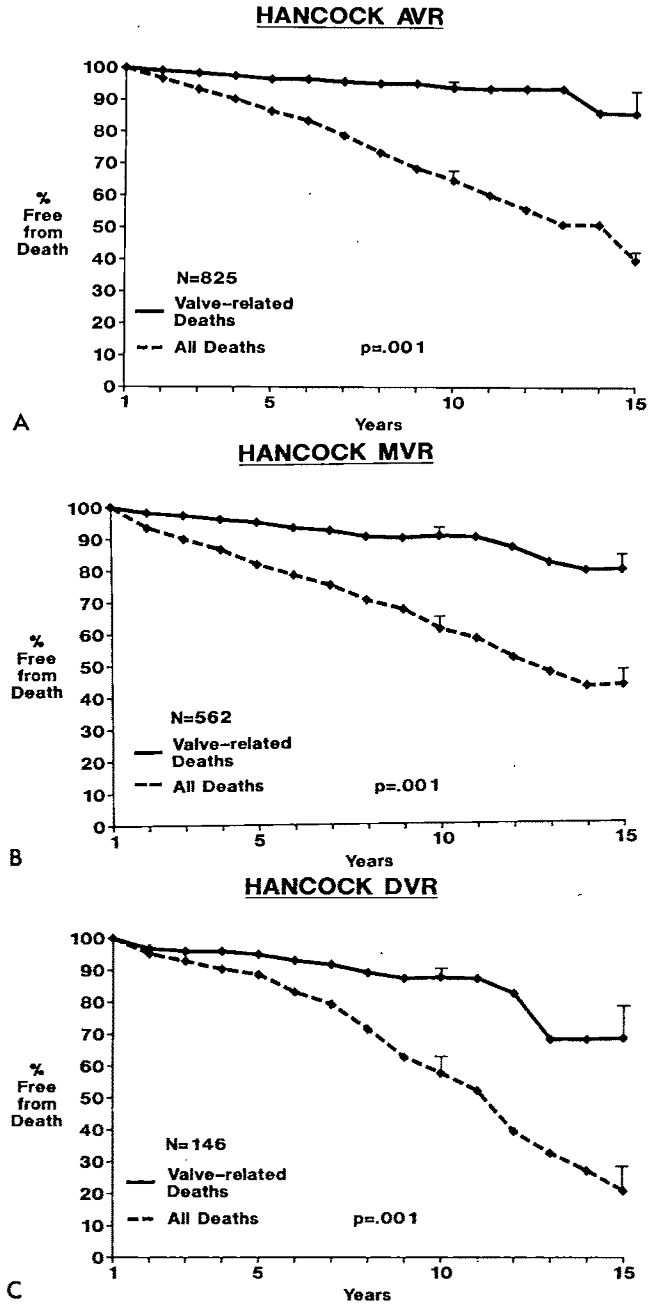


FIGS. 1A–C. The actuarial calculation of patient survival in those patients who survive the hospitalization, separated into valve-related deaths and compared to all valve-related deaths. The p value is 0.001 for all three figures. (A) is AVR, (B) is MVR, and (C) is double valve replacement.

for examination or contacted by telephone, or their doctors were contacted during this period for a detailed questionnaire about their clinical status. Data were entered and maintained on a VAX 11/780 computer (Digital Equipment Corporation, Maynard, MA) running the UNIX operating system using the GDVS interactive data entry system. The database consists of patients who have undergone valve replacement since January 1, 1972. For this analysis the subset of patients who underwent replacement with a Hancock valve between January 1, 1972 and December 31, 1987 was extracted and was 53% of the total valve cohort. The data were moved to a Dell System 310 personal computer (Dell Computer Corporation, Austin, TX) and analysis files with end points, time-to-end points, and appropriate strata were created using SAS (Statistical Analysis System, SAS Institute, Cary, NC). Actuarial Kaplan-Meier survival analyses were performed with the SAS Lifetest procedure and differences in survival among strata were examined with the Wilcoxon and log rank tests. Ten- and 15-year survival estimates and standard errors are reported.

Results

Demographics

Between January 1972 and December 1987, 1678 Hancock valves were implanted in 1533 patients. There were 885 male and 648 female patients ranging in age from 17 to 95 years, with a mean of 60 years. Eight hundred twenty-five patients underwent isolated aortic valve replacement, 562 patients underwent isolated mitral valve replacement, and 146 patients underwent simultaneous aortic and mitral valve replacement. Table 1 also includes the percentage of patients who had concomitant coronary artery bypass grafting. Of the aortic valve group, 28% had coronary bypass; 22% of the mitral valve group had bypass; and 11% of the double valve group underwent bypass. In Table 1 is also shown a percentage of patients with stenotic as opposed to regurgitant lesions and the percentage of patients with preoperative atrial fibrillation or heart block *versus* those in sinus rhythm.

Operative Mortality

The variables that were evaluated in this analysis include overall operative mortality based on the position of

TABLE 1. *Demographics*

Demographic Variable	AVR	MVR	DVR
Number of patients	825	562	146
Sex: M/F	611/214	201/361	72/74
Age range, mean	16–95, 61	17–86, 59	19–79, 59
% of FC 3/4	92	98	94
% of CABG	28	22	11
% of AS/AR	69/31	—	55/50
% of MS/MR	0	50/68	50/54
% preop. AF/HB	10	58	50
% preop. NSR	90	42	50

AVR, Aortic valve replacement; MVR, mitral valve replacement; DVR, double valve replacement; M/F, male/female; F/C, functional class; AS, aortic stenosis; AR, aortic regurgitation; MS, mitral stenosis; MR, mitral regurgitation; AF/HB, atrial fibrillation/heart block; NSR, normal sinus rhythm.

TABLE 2. *Operative Mortality*

Factor	AVR	MVR	DVR
Overall	36/825 (4%)	49/562 (9%)	14/146 (10%)
% with CABG	10%	16%	0
% ≤ 1978	8 } p = 0.01	7 } NS	6 } NS
% > 1978	3	9	11

AVR, Aortic valve replacement; MVR, mitral valve replacement; DVR, double valve replacement.

valve implanted, the time of implantation (1972 to 1977 *vs.* 1978 to 1988) with or without coronary bypass, and the age group of the patient related to mortality, and valve-related morbidity (Table 2).

For the entire group the overall operative mortality rate was 6%, (99 of 1533 patients). The overall mortality rates were 4% for aortic valve replacement, 9% for mitral valve replacement, and 10% for double valve replacement. Of 372 patients who had single or multiple valve replacements in conjunction with one or more coronary bypass afts, there were 26 operative deaths in this group, or an erall mortality rate of 7%. Only in the MVR group was difference in mortality rate significant between those h no CABG (76%) as those with CABG (12.7%); 7.6% = 0.04%) *vs.* 12.7% (p = 0.04).

Operative mortality was analyzed before and after we gan to use cold hyperkalemic cardioplegia in 1978. The operative mortality rate was 8% after AVR before the use of cardioplegia, and 3% following its use (p = 0.01). There was no difference in the operative mortality rate after MVR or DVR before or after the routine use of cardioplegia, except in mitral valves with or without CABG, reported previously.[9]

Operative deaths naturally varied significantly with age. The percentages of operative mortality in the three groups was 2% under 40 years, 4% between 40 and 70 years, and 7% for patients older than 70 years. For mitral valve replacement it was 2% for patients less than 40 years, 9% for patients between 40 and 70 years, and 10% for patients older than 70 years.

The major cause of operative death in this experience was due to cardiac failure manifested by acute low cardiac output, acute myocardial ischemia, or congestive heart failure, the three most common causes of death accounting for over 70% of the postoperative deaths.

Late Mortality

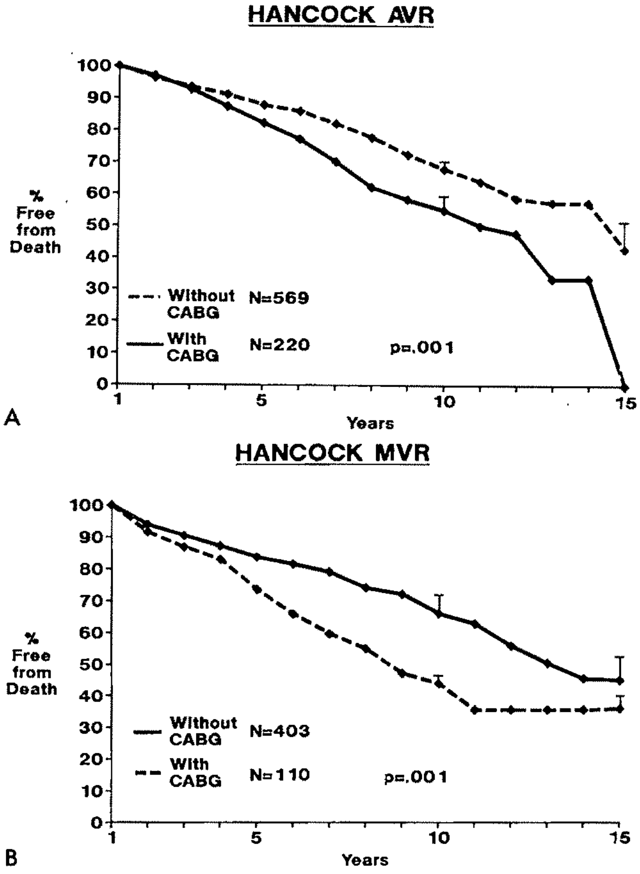
Late deaths again resulted primarily from myocardial factors contributing to congestive failure, severe arrhythmias, and acute myocardial infarction. There were 459 late deaths of which 21% (96 of 459) were noncardiac. Any patient whose cause of death was unknown was considered to be cardiac- and valve-related in origin. The incidence of late death was highest in the group undergoing concomitant coronary bypass. One hundred thirty-six of 459 (or 30%) late postoperative deaths were in patients who had concomitant coronary bypass.

These survival relationships are shown in Figures 1 and 2, acturial fashion after AVR, MVR, and DVR. These curves consider all deaths and valve-related deaths (Fig. 1) and survival with or without coronary bypass (Fig. 2).

As anticipated, the percentage of late deaths in the three age groups (less than 40, 40 to 70, and more than 70 years) correlated directly with increasing age. However there was no significant difference between valve-related deaths by age with the percentages after AVR, 5%, 3%, and 5%, respectively, and after MVR, 4%, 8%, and 8%, respectively.

Postoperative Functional Class

Postoperative functional class was evaluated in all survivors. After AVR 96% of surviving patients were functional classes 1 and 2, while 4% were classes 3 or 4 (Table 3). In this latter group, persistent class 3 or 4 was usually



FIGS. 2A and B. The actuarial calculation of patient survival divided according to whether a concomitant coronary bypass graft was done for coronary artery disease. The probability of survival in the two groups in both the (A) AVR, and (B) MVR is significant to the 0.001 level.

TABLE 3. *Late Follow-up*

Factor	AVR	MVR	DVR
% LTFU	4	5	6
% FC 1/2	96	94	100
% FC 3/4	4	6	0
% postop. AF/HB	19	37	35
NSR	81	63	64

LTFU, lost to follow-up; FC, functional class.

related to longstanding chronic congestive heart failure that did not improve after valve replacement. In patients who were evaluated for postoperative cardiac rhythm, there was a similar percentage after AVR, but after MVR and DVR there was a shift toward a higher incidence of sinus rhythm in the survivors.

TABLE 4. *Probability of Freedom (n = 825)*

Factor	10 Years	15 Years
All death	65 ± 2	40 ± 6
VR death	94 ± 3	86 ± 5
Reoperation	87 ± 2	57 ± 8
SVD	82 ± 2	58 ± 8
TE	86 ± 2	68 ± 8
AcH	98 ± 1	97 ± 1
Thrombosis	99 ± 1	99 ± 1
Hemolysis	99.7 ± 1	99.7 ± 1
IVD	94 ± 1	93 ± 2
PVL	95 ± 1	87 ± 4
All M&M	60 ± 3	49 ± 4
All valve M&M	81 ± 2	54 ± 9

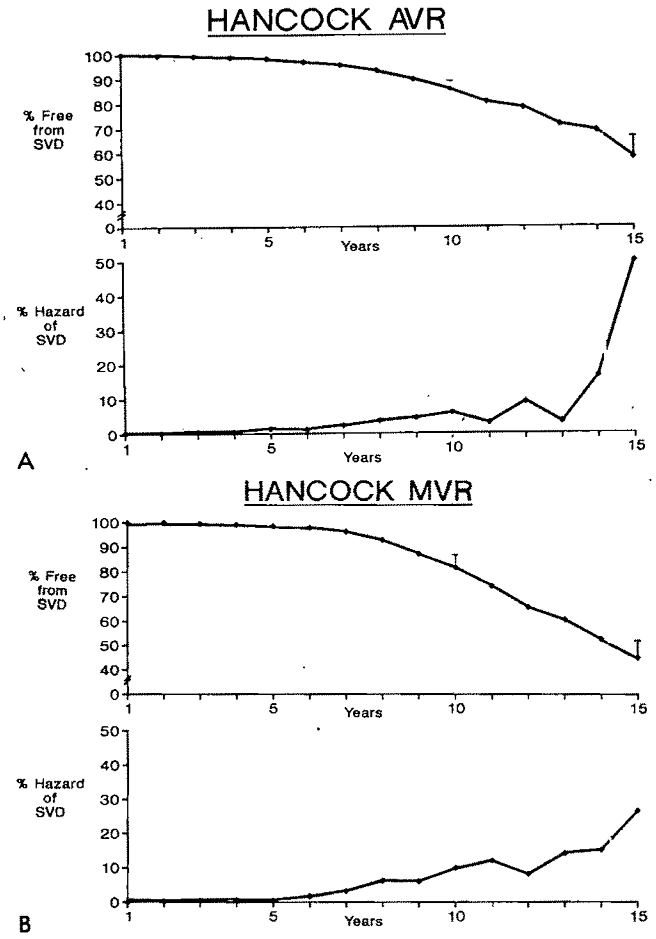
VR, valve related; SVD, structural valve degeneration; TE, thromboembolism; AcH, anticoagulant hemorrhage; IVD, infection valve degeneration; PVL, perivalvar leak.

Structural Valve Degeneration (SVD)

Structural valve degeneration is defined as any change in valve function resulting from an intrinsic abnormality causing stenosis or regurgitation.[10] In the case of the Hancock porcine valve, this usually means calcification, leaflet tear, disruption, or stenosis by stent "creep."[11] It excludes infected or thrombosed valves and was determined by reoperation, autopsy, or clinical investigation. Sixty-eig[illegible] patients after AVR (9%), 73 patients after MVR (14%) and 14 patients after DVR (11%) had SVD.

Figure 3(AVR and MVR) shows the probability of freedom from SVD and the percentage of hazard risk of SVD per year. These calculations indicate that the probability of SVD increases with time, as does the hazard of this complication. The probability of freedom from SVD is noted in Tables 4 to 6 of morbid events associated with each valve. At 10 years this was 82±2 for AVR, 75±3 for MVR, and 89±4% for DVR.

Results of SVD are also correlated with the age of the patient. It has been well documented by a number of previous series that there is a higher rate of SVD in the patients under age 40 years who receive a porcine valve,[12] especially teenagers. Conversely it has been shown that



FIGS. 3A and B. This shows the probability of freedom from structural valve degeneration on the top half of the figures and the per cent hazard of SVD for each year of follow-up in both AVR (Fig. 4A) and MVR (Fig. 4b).

TABLE 5. *MVR: Probability of Freedom (n = 562)*

Factor	10 Years	15 Years
Death	61 ± 3	43 ± 4
VR death	90 ± 2	79 ± 4
Reoperation	79 ± 3	41 ± 7
SVD	75 ± 3	45 ± 7
TE	81 ± 2	70 ± 6
ACH	96 ± 1	94 ± 2
Thrombosis	100	100
Hemolysis	99 ± 1	99 ± 1
IVD	93 ± 2	91 ± 2
PVL	95 ± 2	91 ± 3
All M&M	52 ± 2	28 ± 5
All valve M&M	78 ± 3	66 ± 5

VR, value related; SVD, structural valve degeneration; TE, thromboembolism; ACH, anticoagulant hemorrhage; IVD, infection valve degeneration; PVL, perivalvar leak.

TABLE 6. *DVR: Probability of Freedom (n = 146)*

Factor	10 Years	15 Years
Death	58 ± 5	21 ± 8
VR death	88 ± 3	69 ± 10
Reoperation.	78 ± 5	57 ± 8
SVD	89 ± 4	69 ± 7
TE	91 ± 4	88 ± 5
ACH	94 ± 3	89 ± 6
Thrombosis	99 ± 1	99 ± 1
Hemolysis	100	100
IVD	84 ± 5	76 ± 9
PVL	97 ± 3	97 ± 3
All M&M	62 ± 6	42 ± 7
All valve M&M	80 ± 5	57 ± 11

VR, valve related; SVD, structural valve degeneration; TE, thromboembolism; ACH, anticoagulant hemorrhage; IVD, infection valve degeneration; PVL, perivalvar leak.

SVD is significantly less in the elderly patients who receive a porcine valve.[13] In our series we analyzed all three valve positions for SVD, for ages less than 40 years, 41 to 69 years, and more than 70 years (Fig. 4, Table 7). At 15 years the probability of freedom from SVD is 55% in patients aged less than 40 years, 82% in patients in the 40-to-70 year range, and 90% in patients older than 70 years (Table 7). At 15 years the probability of freedom from SVD in patients less than 40 years for aortic valve replacement is only 35%, *versus* 58% for patients who are 41 to 69 years old, and 90% for the patients who are 70 years or older.

Thromboemboli

Thromboemboli are noninfectious emboli and include all neurologic events noted after operation including transient neurologic findings. As noted in the Tables 4 to 6 and Figure 5 for AVR, MVR, DVR, the risk of thromboembolism varies for each valve type. Thromboembolism is a relatively low risk factor after AVR, notwithstanding that more than 90% of the patients with aortic valve replacement are off chronic anticoagulation therapy. About 50% of patient after MVR or DVR are on anticoagulation therapy.

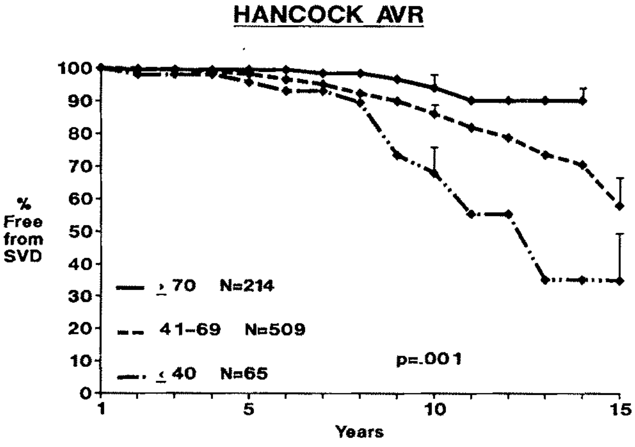


FIG. 4. This figure shows the probability of freedom from structural valve degeneration separated according to the age of the patient at implantation of the aortic valve. The figure shows statistically significant differences between those patients who are 70 years or older compared to those 41 to 69 years and to those who are 40 years or younger. The p value is 0.001.

TABLE 7. *Age* Versus *Incidence of SVD (% Freedom from SVD at 10 Years)*

	≤40	41–69	≥70	p value
AVR	68 ± 9	86 ± 2	94 ± 3	(p = 0.001)
MVR	68 ± 10	84 ± 3	84 ± 10	(p = NS)
DVR	89 ± 10	87 ± 5	100	(p = NS)
All	69 ± 7	85 ± 2	92 ± 3	(p = 0.001)

AVR, aortic valve replacement; MVR, mitral valve replacement; DVR, double valve replacement.

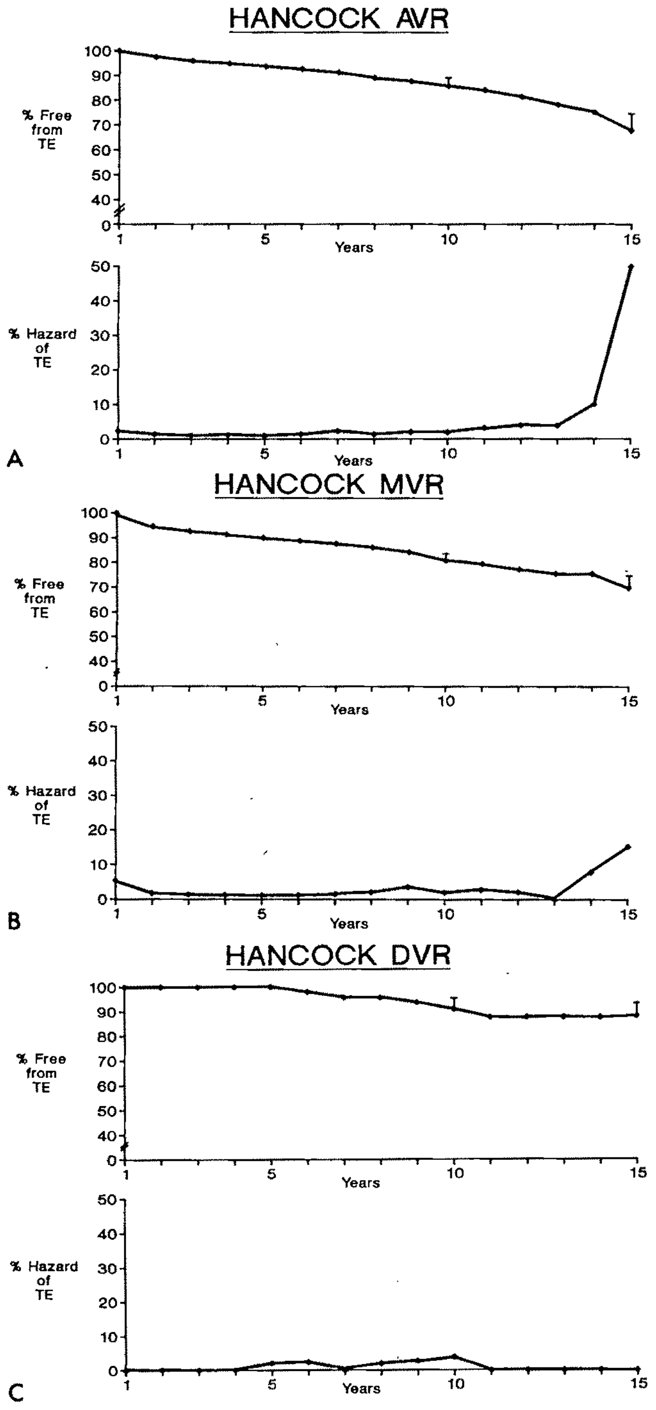
Other Morbidity

Tables 4 to 6 note the risk of thrombosis, hemolysis, infectious valve degeneration, perivalvar leak, and reoperation for each valve. Figure 6 shows the probability of freedom from reoperation at 10 and 15 years, increasing significantly with time. Overall 194 patients had a secondary replacement of a porcine valve with 79 AVR (10%), 91 MVR (16%), and 24 DVR (17%), with 14 mortalities (7%). Finally Figure 7 shows the freedom from all valve-related morbidity.

Discussion

The Hancock valve has proved to be a very important valve replacement device in the treatment of hundreds of thousands of patients with valvular heart disease. At this time after more than 18 years of continuous clinical use, we may state with reasonable certainty its benefits, disadvantages, limitations, and indications for its use. The operative mortality data correlate well with patient variables, especially coronary artery disease, time of operation, and method of myocardial protection, factors that have been previously emphasized.[14,15]

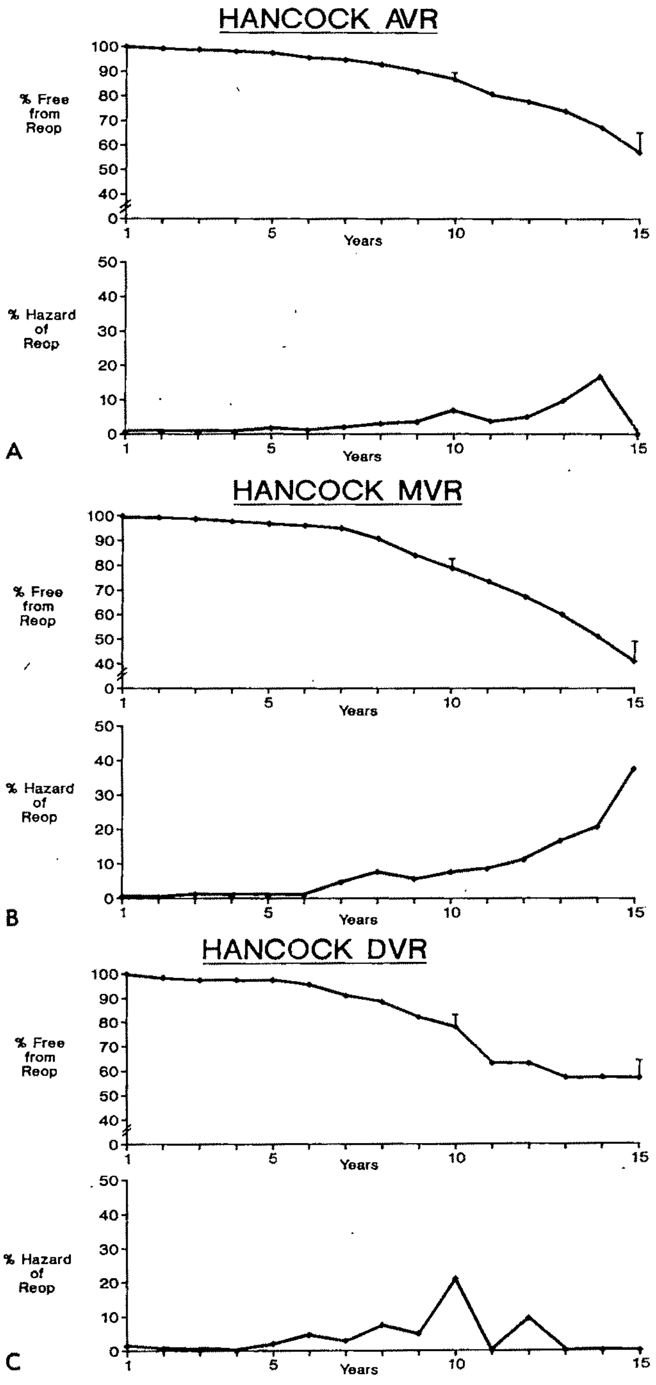
The long-term data presented here correlates with data from other centers.[16–18] Structural valve degeneration is the main risk factor of this valve, as it is with all biologic valves beginning 8 to 10 years after operation. The Glutaraldhyde treatment has markedly improved longevity of porcine valves over formalin-treated valves, but it now appears that in the general adult population in whom it is used the probability of its failure begins to accelerate very markedly at 10 years and rapidly increases at 15 years. When one examines SVD by age categories, it degenerates faster in patients younger than 40 years, but the



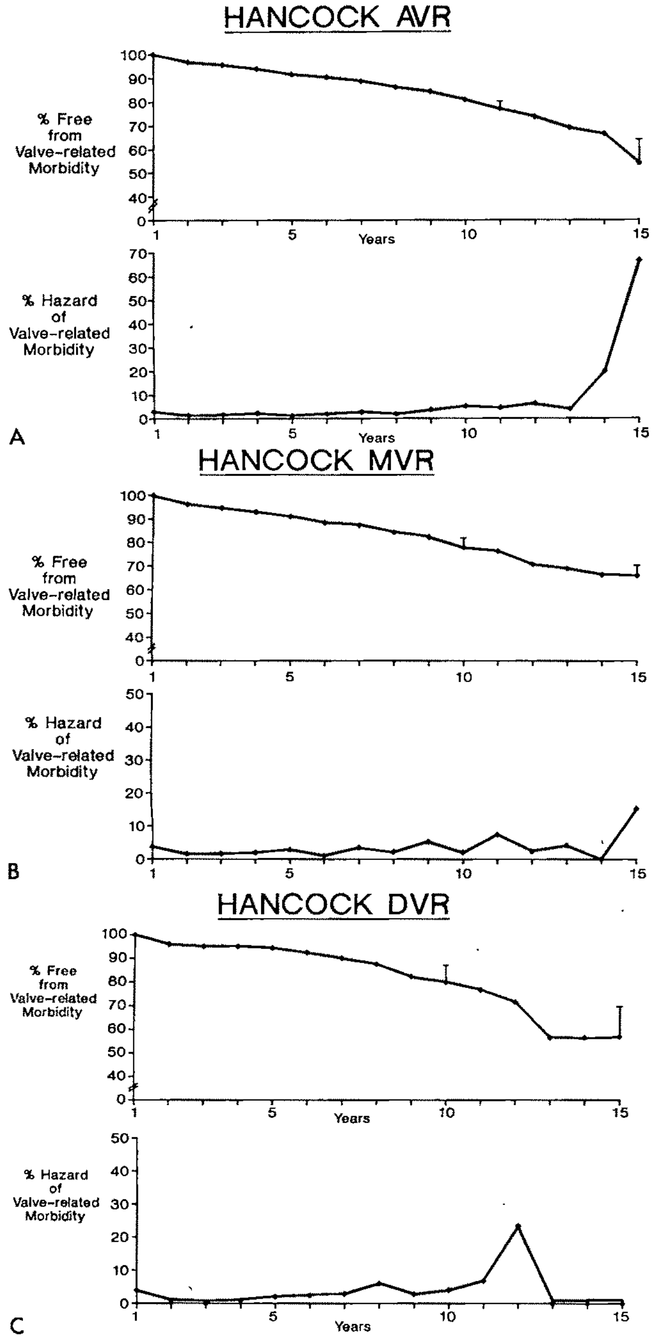
FIGS. 5A–C. Shows the probability of freedom from thromboembolism and the per cent hazard of thromboembolism after (A) AVR, (B) MVR, and (C) DVR.

elderly age group does quite well with this valve and the incidence of SVD is quite low.[7,13]

One of the questions that comes up in analysis of SVD with biologic valves, particularly in long-term data, is whether the incidence of this problem is totally accurate. Despite operative, autopsy, and clinical examinations it is probably not totally accurate as a result of a variety of factors, but certain assumptions have been made in calculations of the data here and may neutralize inaccuracies. For example in the calculation of survival, all deaths that are not known to have a specific cause are considered to be valve related as determined by the joint committee on valve guidelines.[10] Obviously patients who have died and have not been autopsied may have some valvular degen-



FIGS. 6A–C. Shows the probability of freedom from reoperation after (A) AVR, (B) MVR, and (C) DVR.



FIGS. 7A-C. Shows the probability of freedom from all valve-related morbidity in hospital survivors after (A) AVR, (B) MVR, and (C) DVR.

eration and a few will be unknown to us. Most importantly, as Grunkemeir has pointed out (personal communication), patients in our series and other American series may die before the valve degenerates so that valve survival from an acturial standpoint may be higher than it actually would be if all patients survived until their valve degenerated.

The figures presented probably represent the best-case situation given these limitations. The numbers described here are similar to that of Foster et al.[18] (75% freedom at 10 years—MVR). Miller et al.[19] indicate 80% freedom from SVD at 10 years for AVR, and Magilligan[20] reports 10-year freedom from SVD after AVR of 75% and MVR of 65%. The relatively high rate of dysfunction in the younger age groups obviously mitigates its use, except in selected instances in which there are concerns about anticoagulation with prosthetic valves. As follow-up increases in an individual patient, follow-up visits with the patient should be more frequent so as not to miss onset of valve deterioration. We have shown in unpublished observations that if patients are neglected, they may present with "acute" SVD and require urgent operation about 10% of the time.

Thromboembolism in the patient with sinus rhythm is low after use of the Hancock porcine valve. The difficulty with obtaining completely accurate rhythm differentiation did not allow us to separate these patients out in terms of thromboemboli,[14] but in previous experiences AVR and MVR[15] data indicate that this is the case and it is logical to assume that a patient in chronic atrial fibrillation will have a higher incidence of thromboemboli despite anticoagulation. Our current indications for use of the Hancock valve suggests that if a patient is in chronic atrial fibrillation and should require chronic anticoagulation, exposing the patient to the increased risk of structural valve degeneration is not warranted and the patient should have a prosthestic mechanical heart valve. Thromboembolism is probably also under reported because of silent emboli and difficulty obtaining detailed neurologic examinations.[21,22]

The incidence of other comorbidity such as infection, hemolysis, and thrombosis are low with this valve. When calculating all valve-related morbidity and mortality, this valve compares favorably to other reports of prosthestic and bioprosthestic valves.

What are the indications for use of the Hancock porcine valve as we now enter the 1990s? The porcine bioprosthetic valve should be used primarily in the elderly age group. The incidence of structural valve degeneration is significantly reduced in this patient group. The obviation of the use of anticoagulation is also a distinct advantage in the elderly age group because they obviously will have more concomitant medical and surgical problems. However in any patient, regardless of age, in whom long-term anticoagulation is relatively or absolutely contraindicated, it is preferential to use a biologic valve such as the Hancock porcine valve. For example a woman in the child-bearing years who requires valve surgery would be a perfect candidate for this valve inasmuch as Coumadin (DuPont Laboratories, Wilmington, DE) is teratogenic and thus contraindicated and a mechanical valve requires anticoagulation. A patient would have to undergo a second operation in 10 years but has the ability to have children in that interim period with a considerably reduced maternal and fetal risk.

This valve has been shown to have an effective life of about 10 years. However the probability of valve failure is clearly dependent on age and type of use. It has a low incidence of thromboemboli, particularly in the aortic position without anticoagulation. The Hancock porcine valve should be the valve of choice in the elderly age group or in any patient in whom there may be present or future contraindications to anticoagulation from serious medical or surgical problems.

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DISCUSSION

DR. D. CRAIG MILLER (Stanford, California): Today you have heard some new terms, and I rise to compliment Larry and his colleagues for applying most of the new valve-reporting definitions and guidelines recently promulgated by the AATS and STS (as published in *The Journal of Thoracic and Cardiovascular Surgery*, *Annals of Thoracic Surgery*, and *European Journal of Thoracic and Cardiovascular Surgery*). Finally after 3 or 4 years of work on behalf of many individuals, we have a "universal language" to discuss valve complications. The term he used today, structural valve degeneration, or SVD, is all-inclusive with regard to the prosthesis *per se* and has replaced older parlance. Another important aspect of this new scheme is that all sudden, unexpected late deaths are included as valve-related deaths unless proved otherwise. I was interested to see that this did not drop your valve-related death rate curves very much, Larry. You have also conformed to the guidelines by exceeding the minimum 95% complete follow-up threshold; we all know how hard that is when you are talking about 16 years of follow-up.

Indeed we do need to know the clinical performance characteristics of these old "Model T," first generation porcine valves at 15 years. Previously reported series from Detroit and Padua have primarily concentrated on younger patients and many with endocarditis. Many of us have not been certain that these results are truly applicable to the patients you and I see today. My first question is: Will the new porcine valves implanted today (from all manufacturers) perform better in the long term as expected? That is, will the subtle improvements in tissue procurement, preservation, stent design, and quality control procedures actually translate into increased clinical durability?

My second question concerns your belief that this is a "10-year valve" (at least in most patients) and your disappointment at these 15-year clinical results. I would like to propose an alternative reinterpretation of your data that indicates that this valve is actually a reasonable choice for most patients older than 40 years, as manifested by your AVR valve-related death rate of 14% at 15 years (21% for the mitrals). For comparison Dr. Albert Starr just gave me his updated long-term actuarial estimates for the silastic ball valve. After 15 years, the valve-related death rate was 9% for the aortics and 22% (after 20 years) for the mitrals. These figures may actually be somewhat similar to your data. Furthermore 5% of the AVR silastic ball valve patients had required reoperation, as had 25% of the mitral patients; 44% of the AVR and 33% of the MVR patients had had an anticoagulant-related bleed; and 16% and 55%, respectively, had sustained a thromboembolic complication.

I was pleased to see that you alluded to Gary Grunkemeier's and Albert Starr's application of the Weibull equation, which is an engineering method used to examine questions of failure analysis as a function of time. The key point here is that 15 years may be more than several potential lifetimes for many of our patients. I believe all of us should consider this when we discuss long-term valve durability.

I also have some questions pertaining to your age information. (1) I was interested to note that there was no difference in valve-related death rates according to age; perhaps you could elaborate on this intriguing observation. (2) In terms of what specific threshold age below which the durability of a porcine valve will not meet the patient's or the surgeons's expectations, all of us have the same problem in that nobody has 100 or so patients operated on at each year of age across the spectrum; this sampling problem leads to skewed patient populations, so we may never be able to say with certainty which exact age is too young for a patient to receive a porcine valve. (3) If you look at your incidence of porcine valve SVD as a function of age, it was not statistically higher for the younger MVR patients, just for the aortics. Would you comment on this interesting finding?

When you described the rather alarming jumps in the hazard functions at 14 to 15 years, I am afraid that the very small number of patients remaining at risk cripples any meaningful inference one can make from the data. Perhaps you should "back off" these figures for a couple of years such that you would have larger numbers of patients at risk and add confidence levels (or SEMs) as an indication of variability. And finally would you speculate on whether "unnatural selection" has any chance of actually making these late increases in the hazard function for SVD level off (or possibly decline) as those who do not do well with their porcine valve have it removed over time, thereby leaving a highly selected subset of patients remaining at risk long after operation?

DR. GEORGE J. MAGOVERN (Philadelphia, Pennsylvania): Dr. Cohn has presented a careful review of the more than 1500 patients receiving more than 1500 bioprosthetic valves during a 15-year period, either aortic, mitral, or double valve replacements. He has then further divided that group of patients according to whether they received saphenous bypass grafting, and then in the postoperative period has examined some 12 variables.

This is a monumental amount of data to digest and I would only assure you that it is a very definitive paper because of the amount of information that will require careful scrutiny. I was privileged to have reviewed it briefly.

I am pleased that they presented the findings as they did because I do think having 30 patients followed for 10 years is better than having 300 patients followed for 1 year when we are considering patient years. That is a big difference and has been one of the problems in reporting valve mortality and morbidity rates. Dr. Cohn has carefully addressed that. His group certainly deserves accolades in many regards. They are one of the principal groups in the country for tissue valve follow-up.

Several points need to be stressed, however, in the paper. One is that the results are positively stated, which is good; if you have a 70% survival rate or 70% thromboembolic-free rate, it means that you had 30% of the patients who did have a thromboembolism, and so that is significant.

But as he points out, most of the structural problems of performing these and the complications occur after 10 years, so my first question then is: do you advise elective valve replacement on these patients after a specific period of time, and when and on whom would you advise it? And also have you correlated your structural valve degeneration with the size of the valve? It has certainly been our experience that if you have a smaller valve, the surface area and the pressure is distributed differently over a smaller valve than a larger valve, and that deformity and destruction tends to be greater in the smaller valve. We usually opt for a mechanical prosthesis in the small aortic root, for instance.

The other point I would like to stress is that although your operative mortality rate was remarkably low, 2% in those under 40 years of age and only 2% to 4% in those under 70 years of age, it was 13% in patients who had mitral valve disease and coronary revascularization, and as you pointed out on the slide, most of those patients did not survive more than 10 years.

The point is do you believe that valvuloplasty in this ischemic myocardium-related valve problem represents perhaps a better solution than has been reported by Cosgrove and others?

And finally because you have only used the bioprosthesis in 50% of your patients, do you think this skewed your statistics in any way?

DR. LAWRENCE H. COHN (Closing discussion): I thank Drs. Miller and Magovern for reviewing our manuscript and all of these statistics last night. I appreciate their questions, all of which are very germane.

Let me tackle the many excellent questions of Dr. Miller first. Many of these patients and valve variables, between 10 and 15 years, decrease in number, and that is one of the problems in this whole field; that is why I showed that slide by Gary Grunkmeier to illustrate that when you get out to the late years with small numbers, a single event can make a dramatic change in a morbid-event curve. I would have to answer most of your questions about these variables by stating that if we can get more numbers in that area we will have better data, but as noted, this may be impossible due to the advanced age of patients and their deaths from other causes. We may never actually know the true answer to some of the questions that you have asked at the 15+ year level. Our results and yours are better than many European studies because the mean age of U.S. series is 10 to 15 years older than that of European series.

You asked about new bioprosthetic valves. New preservation and fabrication techniques would seem to suggest that these new porcine valves will be better. These will have to stand the test of time, as determined by statistical analyses presented here confirming to the reporting guidelines set up by the AATS/STS.

Your questions about valve-related death are important and suggest that this is a good valve for all adults with the exception that in the younger age groups reoperation is inevitable. The reoperative mortality rate of 7% included mostly one and two reoperations. We have seldom put in more than two separate porcine valves because our patients do not wish to undergo a third or fourth reoperation, despite the advantages of no anticoagulation and low thrombogenic potential. I can not explain the age-related data on mitrals. Overall age was a significant factor in SVD, as it also was in the aortic group, *i.e.*, younger patients had higher SVD rates.

Your comment regarding length of follow-up and hazard curves is relevant because the confidence levels are wide at 13 to 15 years, but many statisticians believe all the data should be presented, not just at 10 or 12 years, and we have done so. Perhaps a dashed line after 12 years would be preferable.

To Dr. Magovern, thank you for your comments. We did not correlate any variable with the size of the valves, but we don't implant any biologic valves less than 21 mm in diameter. Not noting any obvious correlation, we will have to go back and look at size and variables again. You asked about coronary bypass and mitral valve replacement, a very high risk group. I absolutely support your conclusion and we have published recent papers about our position that valvuloplasty with preservation of the papillary muscle-annular continuity for mitral regurgitation is the way to go, and we have been actively doing this in the past 5 years. It might be noted that the higher mortality rate in the valve replacement group has been mitigated, to a certain extent, by the change in myocardial protection, remembering that this series dates from 1972. About midway (1978) we switched to crystalloid cardioplegia, and we know that in the elective mitral valve coronary bypass group, with the use of cardioplegia, the operative mortality rate in the MVR/CABG group fell to about 4%.

The Clinical Management of a Normal Contralateral Breast in Patients with Lobular Breast Cancer

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Ninety-nine patients with the diagnosis of lobular carcinoma (LC) treated between 1970 and 1981 were reviewed. Thirteen patients had a contralateral mastectomy for duct cancer (DC) before the diagnosis of LC. Ten of the remaining 86 patients (11%) had simultaneous bilateral cancers detected by either physical examination or mammography, none by blind biopsy. Three of the surviving 38 patients (7.8%) developed a contralateral cancer an average of 143 months after operation. In comparison 167 patients with DC treated during the same period of time had a 1.8% incidence of synchronous cancer but the same incidence of subsequent cancer (7%). Lobular carcinoma *in situ* was not a reliable marker for predicting the presence of cancers in the contralateral breast. The diagnosis of LC is not an indication for either biopsy or removal of a normal contralateral breast.

From the Departments of Surgery and Pathology, Johns Hopkins University School of Medicine, Baltimore, Maryland

THE CLINICAL MANAGEMENT OF patients with invasive lobular carcinoma of the breast is controversial. Some authors advise routine biopsy of a normal contralateral breast, while others advocate a prophylactic contralateral mastectomy. In contrast Fisher[1] advocates nothing more than routine follow-up of the contralateral breast of the patient with invasive lobular carcinoma. This study was designed to determine the long-term clinical course of patients with invasive lobular carcinoma of the breast and thus further define indications for biopsy or excision of a contralateral breast that is normal on physical examination and mammography.

Clinical Material

The surgical pathology files between 1971 and 1980 were reviewed for all patients with diagnosis of either pure lobular carcinoma (LC) or lobular carcinoma with duct features (LC/DC). On review of the histologic sections of the primary tumor, a diagnosis of LC (69 cases) or LC/DC (30 cases) was confirmed in 99 patients. The histologic sections of these 99 patients were also reviewed to determine the incidence of lobular carcinoma *in situ* (LCIS) in association with a diagnosis of LC or LC/DC. As a control group, 167 patients who survived for 120 months with infiltrating duct cancer (DC) were randomly pulled from the Tumor Registry files between 1970 and 1975. The histologic sections were reviewed to confirm the diagnosis and these patients were followed for an average of 144 months.

At the time of the diagnosis of lobular carcinoma, the 99 patients ranged in age from 30 to 70 years (average age, 54 years). Before treatment the contralateral breast was examined by physical examination and the majority of patients had a mammogram. All patients had a chest x-ray and a serum alkaline phosphatase determination. Scintiscans of the liver and bone were not performed on a routine basis. Two patients with synchronous cancers had either radiographic or scintiscan evidence of systemic metastasis on initial evaluation. None of the remaining 97 patients had clinical or radiographic evidence of systemic metastasis. With the exception of the two patients with systemic metastasis, all patients were treated by modified radical mastectomy or radical mastectomy.

Results

The incidence of synchronous or asynchronous invasive carcinomas in the contralateral breast of these patients is reviewed in Table 1. There was no statistically significant difference between the incidence of bilaterality in patients

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TABLE 1. *Invasive Lobular Carcinoma and Invasive Lobular/Duct Carcinoma Incidence of Bilaterality*

Lobular Carcinoma (n = 69)	
20/69 (28%) with bilateral disease*	
10 previous	(10 DC)
7 simultaneous	(6 DC, 1 LC)
3 subsequent	(2 DC, 1 LC)
Lobular/Duct Carcinoma (n = 30)	
6/30 (20%) with bilateral disease*	
3 previous	(3 DC)
3 simultaneous	(1 DC, 2 LC)

* There was no statistically significant difference in the incidence of bilaterality between invasive lobular and invasive lobular/duct carcinoma.
DC, infiltrating duct cancer; LC, infiltrating lobular cancer.

with LC compared to LC/DC ($p < 0.4$).* In view of these similar clinical courses, the two groups were combined for further analysis.

Thirteen of the 99 patients had a contralateral mastectomy for DC 10 to 168 months (average 74) before the diagnosis of LC. Eight of these patients survived for an average of 88 months without evidence of recurrence after treatment for LC in the ipsilateral breast. Four patients died of metastatic breast carcinoma 24 to 144 months after operation and one died of unrelated causes.

Ten of the remaining 86 patients had simultaneous carcinomas in the contralateral breast (seven DC, three LC). Six of the simultaneous contralateral carcinomas were detected by physical examination, four by mammography alone. Two of these patients had radiographic or scintiscan evidence of metastasis on initial clinical assessment and died 41 and 70 months after initial clinical assessment. Seven of the remaining nine patients died an average of 66 months after operation, and one remains alive 89 months after operation.

Thirty-eight of the remaining 76 patients who survived the initial tumor were followed for 70 to 174 months (average 106 months). Three patients developed a subsequent carcinoma in the contralateral breast 113, 156, and 161 months after treatment of the initial lobular carcinoma (one DC, two LC). One patient has survived for 37 months without evidence of metastasis, and the other two patients died 10 and 36 months after operation of systemic metastasis.

Of the 99 cases reviewed, 61 (61%) had evidence of LCIS in the ipsilateral breast. The influence of LCIS on the incidence of bilaterality is reviewed in Table 2. There was no correlation between the incidence of LCIS in the ipsilateral breast and the incidence of synchronous or asynchronous invasive carcinomas in the contralateral breast ($p < 0.17$).

TABLE 2. *Influence of Lobular Carcinoma* in Situ *on Bilaterality*

Total number of cases with LCIS	61 (61%)
Total number of cases without LCIS	38 (38%)
Incidence of bilateral disease in cases with LCIS	14/61 (22%)
Incidence of bilateral disease in cases without LCIS	12/38 (31%)

LCIS, Lobular carcinoma *in situ.*
These differences were not statistically significant.

The clinical course of 167 patients with DC as compared to that of patients with LC is reviewed in Table 3. The incidence of simultaneous primary carcinomas was significantly increased in those patients with LC. The incidence of subsequent carcinomas in the contralateral breast was essentially equal in patients with LC compared to those with DC.

Discussion

Invasive lobular cancer is not a common tumor. Fisher[2] reports an 8.2% incidence of LC or LC/DC in a series of 1000 cases of invasive breast carcinoma. In Fisher's experience[2] these tumors were not multifocal in origin, all of the lobular carcinomas were confined to the quadrant containing the palpable mass, and there was no evidence of microscopic tumor in quadrants remote from the quadrant of origin. In spite of these histologic observations, there is a 25% clinical incidence of either synchronous or asynchronous carcinomas in the contralateral breast of patients with LC and an even higher incidence of LCIS. The relationship between LCIS and LC remains somewhat obscure. The two lesions are frequently seen together but a number of studies have demonstrated that LC can be present alone. The clinical behavior of LC *versus* LCIS is also considerably different. LC is a malignant tumor with the same potential for metastasis as DC

TABLE 3. *Bilaterality and Invasive Carcinoma*

Contralateral Breast	Lobular Cancer (n = 99)	Infiltrating Duct Cancer (n = 167)	p value
Simultaneous primaries	10/99 (10%)	2/167 (1.2%)	< 0.0003
Subsequent primaries	3/38 (7.8%)	14/165 (8.3%)	< 0.04
Previous infiltrating duct carcinoma	13/99 (13%)	NA	
Total	26/99 (26%)	16/167 (9.5%)	< 0.0001

NA, not applicable.

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* Statistical evaluations were done by Fisher Exact Test.

TABLE 4. *A Comparison of Results of Ashikari's Study with Current Study—Lobular Carcinoma*

Contralateral Breast	Ashikari's	Current Study
Contralateral cancers	79*/349: 23%	26/99: 26%
Previous	21 (26%)	13 (50%)
Simultaneous	28 (35%)	10 (38%)
Subsequent	30 (38%)	3 (12%)

* 25% LCIS.

in contrast to LCIS, which is a premalignant lesion. Patients with histologic evidence of LCIS alone have a 25% chance of developing either a DC or LC in either breast within the next 25 years. We would agree with Fisher[1] that a number of clinical series discussing the bilaterality of LC have included a significant number of patients in whom the tumor in the contralateral breast has been LCIS.

Because LC is a relatively uncommon lesion there are not a large number of clinical cases reported in the literature. Ashikari[3] reports the largest series of patients with LC, 349 patients with a 23% incidence of either synchronous or asynchronous carcinoma in the contralateral breast. Although 25% of these patients had only LCIS in the contralateral breast, the overall results were similar to the current study (Table 4). We must then address the issue as to how this 25% incidence of bilateral disease should affect the clinical management of a normal contralateral breast in patients with LC.

As previously noted any discussion of the clinical management of LC is complicated by the relatively small number of cases in any one series and the tendency of some authors to refer to LCIS as if it were an invasive lesion. Some authors advise biopsy of the contralateral breast in patients with LC. Donegan[4] describes a group of 36 patients with LC and/or LCIS. Although none of the patients with LC had a simultaneous biopsy of a normal contralateral breast, the authors advise biopsy of a normal contralateral breast in patients with LC. In evaluating the use of a contralateral biopsy in a large number of patients with invasive breast carcinoma, Anderson[5] describes a 50% incidence of a positive biopsy in six patients with LC. However all the contralateral biopsies revealed LCIS rather than invasive carcinoma. Wilson and Alberty[6] report that each of their five patients with lobular carcinoma developed a contralateral carcinoma and therefore advocate biopsy of the contralateral breast. Newman[7] advocates a biopsy of the contralateral breast on the basis of his experience with 67 patients with LC, 10% of whom developed a contralateral invasive carcinoma within 13 to 80 months of the initial lesion.

Benfield[8] and Warner[9] advocate a prophylactic contralateral mastectomy in patients with LC, both authors basing their conclusions on the same group of patients. Although they describe a 70% incidence of multicentricity and a 59% incidence of bilaterality in patients with LC, their statistics appear to be based predominantly on patients with LCIS. Only seven patients with LC are described in either publication. McCredie[10] also advocates a prophylactic contralateral mastectomy based on the fact that 2% of the patients in their experience with subsequent carcinoma in the contralateral breast had LC. Fechner[11] describes a group of 35 patients with LC, five of whom developed an invasive carcinoma in the contralateral breast. Two of these carcinomas occurred within 5 months of the diagnosis of LC in the ipsilateral breast, two within 35 months, and one 14 years later. On the basis of this experience, he advocates excision of a normal contralateral breast in patients with LC. Although Davis[12] does not specifically advocate a biopsy or contralateral mastectomy in patients with LC, he presents perhaps the most convincing data for such an approach. He describes 48 patients with LC, 19 of whom had "an operative evaluation of the opposite breast." Almost 50% of these 19 patients were found to have invasive cancer in the contralateral breast. The exact status of the opposite breast is not described, *i.e.*, its normalcy on physical examination and mammography.

Although our experience with LC is somewhat muted by a high incidence of previous DC, we would agree with Fisher[1] that there is no indication for routine biopsy or excision of a normal contralateral breast in patients with LC. Management of the contralateral breast will not be an issue if it has been previously removed for DC. The presence of LCIS in the ipsilateral breast did not prove to be a reliable indicator of either synchronous or asynchronous cancer in the contralateral breast and therefore could not be used as an indication for biopsy of a normal contralateral breast. None of the normal contralateral breasts in this series were biopsied. We have concluded that we did not miss occult invasive carcinomas in the contralateral breast because subsequent carcinomas, if they did occur, were detected at least 9 years later. This series confirms the fact that synchronous carcinomas are considerably more common in patients with LC compared to patients with DC. Although subsequent carcinomas did occur in the contralateral breast of patients with LC, their occurrence was remote and their incidence was similar to the number of subsequent carcinomas that occurred in patients with DC.

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DISCUSSION

DR. CHARLES M. BALCH (Houston, Texas): I rise to support the basic conclusions that Dr. Baker has made. I would mention, however, that the incidence of invasive carcinoma in the opposite breast does increase as a function of time and follow-up. Some of those studies, both from Memorial Institute and our own, have shown that the incidence of invasive cancer continues to increase over time so that at 20 years it may be as much 15%; however it may still be relatively low at 4% to 5% after only 10 years of follow-up.

There is controversy about the management of the opposite breast because the number of patients is so small. We still do not know whether there are any risk factors that can portend a high probability of developing a second cancer in the opposite breast of a patient with lobular carcinoma of the breast.

One aspect of this problem that was analyzed at the M. D. Anderson Cancer Center involves the geometric location of opposite breast cancers. As you recall it was about 20 years ago when a routine biopsy of the opposite breast was advocated by many surgeons, and if a blind biopsy was done, it should be performed at the "mirror image" location. In fact, our analysis of opposite breast cancer showed that there was no geometric relationship whatsoever. The majority of second carcinomas were located in the upper outer quadrant or the central area. For example, an inner quadrant lesion on one side would not portend an inner quadrant lesion on the opposite side.

Furthermore we would make some distinction between a sparse amount of LCIS around the tumor or elsewhere in the breast and extensive LCIS and have used this as one criteria for biopsies of the opposite breast. This would be especially true in situations in which the opposite breast was difficult to follow because of underlying fibrocystic disease, the patient was unable to have regular follow-up exams, or there was significant and genuine cancer phobia.

The point I would like to make is that if one is going to perform opposite breast biopsies, they should be done sparingly and should not be directed to a mirror image location but in the upper outer quadrant of the opposite breast.

I had three questions I wanted to ask Dr. Baker. First are there any subsets of patients who are at higher risk for developing an opposite breast cancer in their study? Second did they find, as we did, any lack of geometric relationship between the opposite breast cancers? Finally if one is conservative in following these patients without biopsies or mastectomies, it presumes that the screening process would detect an opposite breast cancer at an early and highly curable stage. So my third questions is: In those patients who developed opposite breast cancer, what was the stage and survival of those patients who were followed?

DR. ROBERT P. HUMMEL (Cincinnati, OH): I just rise to make a few comments. The first is that I would certainly agree with Dr. Baker's bottom line that invasive carcinoma of the breast, be it lobular or ductal, seems to act the same. We have reviewed our cases at the Breast Consultation Center in Cincinnati and find that the incidence of bilaterality, lymph node metastases, and so on, is similar once the tumors are invasive.

One of my questions is an elaboration of Dr. Balch's question. It would seem that the recommendations in this paper are based on the ability to follow these patients closely for any recurrent tumor because the percentage of recurrence is high over a period of a number of years. We know there may be a number of difficulties in following patients, including lack of patient follow-up cooperation and the difficulty of evaluating the breast on physical exam. Other patients have difficult mammograms to read. Others have strong family histories of carcinoma of the breast or may show on their biopsy extensive wide-spread dysplasia in the breast specimen along with the original lobular carcinoma. So my question is: Are you influenced by these factors in your recommendations to the individual patient, or do you follow them all regardless of the circumstance?

The other question I would have is that it would seem to me there is even more controversy as to how to treat lobular carcinoma *in situ*, not only in the opposite breast but the same breast. Are you satisfied with a lumpectomy alone or do you recommend any further treatment? I wondered if, after going through these data and looking at your experience with lobular carcinoma both *in situ* and invasive, you have any recommendations about the *in situ* variety of the disease?

DR. FRANK E. GUMP (New York, New York): I would like to congratulate the authors for looking at this topic since it has fallen out of favor in the age of breast preservation.

The series at Columbia is very similar in the sense that we have about the same number of patients, and the only difference has to do with the way that we have looked at the relationship of lobular carcinoma *in situ* to the question of the opposite breast.

I think one of the major differences is the way in which we presented our data. Percentages are very dependent on length of follow-up. If you look at the observed-to-expected ratio, you cannot only deal with that problem, but you can also deal with other risk factors such as family history and patients' ages, which would be important considerations.

The patients who had pure lobular lesions in our series had a 3- to-1 observed-to-expected risk ratio, and this was no different than some 3000 patients who had ductal carcinoma. The difference, though, was in patients who had both the invasive lobular and the *in situ* lobular lesions; here the ratio was 8 to 1. In other words, there was a clear difference when this was added to the invasive lesion. In that sense, we would not agree that the presence of lobular carcinoma *in situ* does not influence the risk on the opposite side. However before closing these remarks, I should say that the same 8-to-1 ratio is true whether you add the lobular *in situ* lesion to an invasive lobular or a ductal lesion, so this is simply a reflection of this marker of increased risk, which is the way we have always looked at lobular carcinoma *in situ.* In fact Dr. Haagensen wanted us to call it lobular neoplasia.

DR. JOHN S. SPRATT (Louisville, Kentucky): I have just a comment and a question. In looking at asynchronous cancers, it is very important to look at the incidence per age-specific man years of observation. This has been shown by the classic work by Schoenfield on multiple primary cancers, and we used the same methodology at the cancer hospital in

Missouri. When you do it this way, you will find in comparing it with the expected incidence in the general population, you will generally find that there is very little difference between the expected and the predicted incidence, the only exception being a slightly greater risk of additional cancers if the first cancer occurs before age 50.

I wanted to ask the authors if they have looked at the asynchronous cancers, the age-specific incidence of asynchronous cancers over time as opposed to just the cumulative numbers where there is no correction for age and man years of observation?

DR. R. ROBINSON BAKER (Closing discussion): I would like to thank all the discussants. In answer to Dr. Balch's questions: we could not identify a subset of patients at higher risk for developing breast cancer. The majority of second cancers, either previous, simultaneous, or subsequent lesions were in the upper outer quadrant of the contralateral breast. We found no geometric relationship between the tumors. Survival patterns were interesting. Those patients who developed a lobular carcinoma after a duct cancer did rather well, with a 60% long-term survival rate. In contrast only one of ten patients with simultaneous lobular carcinoma were long-term survivors and two of three of the patients with subsequent cancers had died of metastatic cancer within 36 months of the diagnosis of the second cancer.

To answer Dr. Hummel's question concerning the management of the contralateral breast in patients with lobular carcinoma, I would make the following comments. Patients with lobular carcinoma are difficult to follow. It is an infiltrative process, not a discrete lesion, and therefore difficult to diagnose by physical examination or mammography. On the basis of our experience, I don't believe the incidence of contralateral cancer is high enough to warrant a routine prophylactic contralateral mastectomy. However because these tumors are difficult to detect by physical examination and mammography, the entire problem should be discussed with the patient and if she prefers to have a contralateral mastectomy, knowing the risk involved, I would agree. In answer to the second question, I believe that patients with the diagnosis of lobular carcinoma *in situ* have a 25% chance of developing an invasive cancer in either breast within the next 25 years. The invasive cancer may be a lobular cancer; it is more frequently an infiltrating duct cancer. Further management, again, is dependent on careful discussions with the patient. I think the only alternatives are follow-up physical examinations and mammography or bilateral mastectomies. The patient should be offered simultaneous reconstruction.

Dr. Gump's comments about the increased risk of contralateral cancer in patient's with infiltrating duct cancer in association with lobular carcinoma *in situ* are interesting. We are currently looking at our overall experience with lobular carcinoma *in situ* and perhaps we will come up with the same results. Unfortunately the presence of lobular carcinoma *in situ* in association with invasive lobular carcinoma did not prove to be a reliable indicator of cancer in the contralateral breast.

Dr. Spratt you raise an interesting complicated question that time does not permit answering. Perhaps we can discuss this independently later this afternoon.

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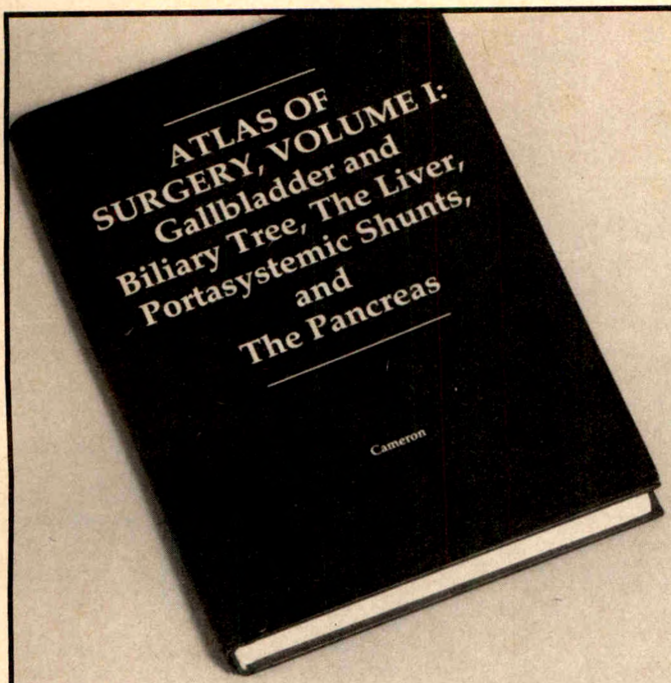
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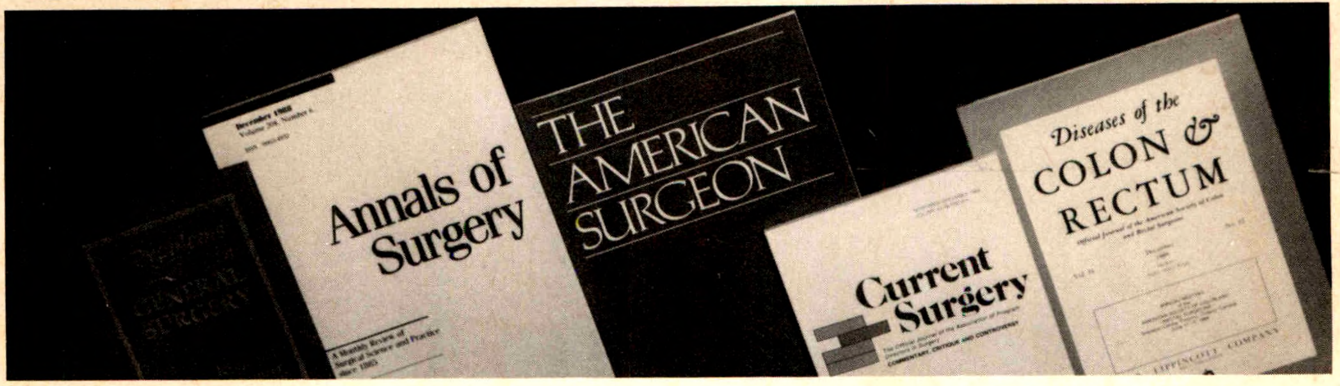

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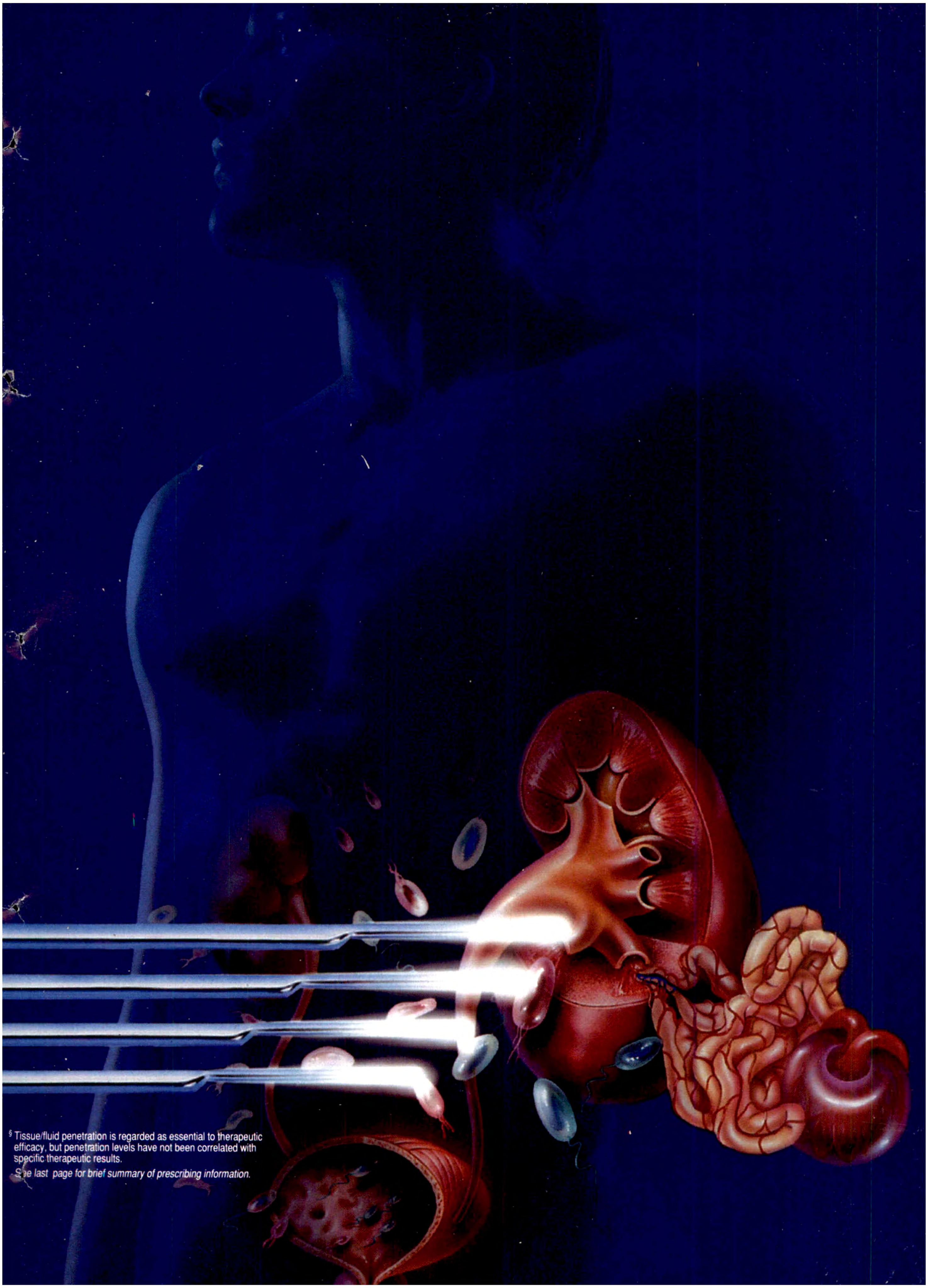

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PRECAUTIONS

General: As with other quinolones, ciprofloxacin may cause central nervous system (CNS) stimulation, which may lead to tremor, restlessness, lightheadedness, confusion, and rarely to hallucinations or convulsive seizures. Therefore, ciprofloxacin should be used with caution in patients with known or suspected CNS disorders, such as severe cerebral arteriosclerosis or epilepsy, or other factors which predispose to seizures (SEE ADVERSE REACTIONS).

Anaphylactic reactions following the first dose have been reported in patients receiving therapy with quinolones. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial edema, dyspnea, urticaria, and itching. Only a few patients had a history of hypersensitivity reaction. Anaphylactic reactions may require epinephrine and other emergency measures. Ciprofloxacin should be discontinued at the first sign of hypersensitivity or allergy.

Severe hypersensitivity reactions characterized by rash, fever, eosinophilia, jaundice, and hepatic necrosis with fatal outcome have been reported rarely (less than one per million prescriptions) in patients receiving ciprofloxacin along with other drugs. The possibility that these reactions were related to ciprofloxacin cannot be excluded. Ciprofloxacin should be discontinued at the first appearance of a skin rash or any sign of other hypersensitivity reaction.

Crystals of ciprofloxacin have been observed rarely in the urine of human subjects but more frequently in the urine of laboratory animals (SEE ANIMAL PHARMACOLOGY SECTION IN FULL PRESCRIBING INFORMATION). Crystalluria related to ciprofloxacin has been reported only rarely in man, because human urine is usually acidic. Patients receiving ciprofloxacin should be well hydrated, and alkalinity of the urine should be avoided. The recommended daily dose should not be exceeded.

Alteration of the dosage regimen is necessary for patients with impairment of renal function (SEE DOSAGE AND ADMINISTRATION).

As with any potent drug, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic function, is advisable during prolonged therapy.

Drug Interactions: As with other quinolones, concurrent administration of ciprofloxacin with theophylline may lead to elevated plasma concentrations of theophylline and prolongation of its elimination half-life. This may result in increased risk of theophylline-related adverse reactions. If concomitant use cannot be avoided, plasma levels of theophylline should be monitored and dosage adjustments made as appropriate.

Quinolones, including ciprofloxacin, have also been shown to interfere with the metabolism of caffeine. This may lead to reduced clearance of caffeine and a prolongation of its plasma half-life.

Antacids containing magnesium hydroxide or aluminum hydroxide may interfere with the absorption of ciprofloxacin resulting in serum and urine levels lower than desired; concurrent administration of these agents with ciprofloxacin should be avoided.

Concomitant administration of the nonsteroidal anti-inflammatory drug fenbufen with a quinolone has been reported to increase the risk of CNS stimulation and convulsive seizures.

Probenecid interferes with the renal tubular secretion of ciprofloxacin and produces an increase in the level of ciprofloxacin in the serum. This should be considered if patients are receiving both drugs concomitantly.

As with other broad-spectrum antibiotics, prolonged use of ciprofloxacin may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition and microbial susceptibility testing is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Information for Patients: Patients should be advised that ciprofloxacin may be taken with or without meals. The preferred time of dosing is two hours after a meal. Patients should also be advised to drink fluids liberally and not take antacids containing magnesium or aluminum.

Patients should be advised that ciprofloxacin may be associated with hypersensitivity reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash or other allergic reaction.

Ciprofloxacin may cause dizziness or lightheadedness; therefore patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or coordination.

Patients should be advised that ciprofloxacin may increase the effects of theophylline and caffeine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Eight in vitro mutagenicity tests have been conducted with ciprofloxacin and the test results are listed below:

Salmonella/Microsome Test (Negative)
E. coli DNA Repair Assay (Negative)
Mouse Lymphoma Cell Forward Mutation Assay (Positive)
Chinese Hamster V_{79} Cell HGPRT Test (Negative)
Syrian Hamster Embryo Cell Transformation Assay (Negative)
Saccharomyces cerevisiae Point Mutation Assay (Negative)
Saccharomyces cerevisiae Mitotic Crossover and Gene Conversion Assay (Negative)
Rat Hepatocyte DNA Repair Assay (Positive)

Thus, two of the eight tests were positive, but the results of the following three *in vivo* test systems gave negative results:

Rat Hepatocyte DNA Repair Assay
Micronucleus Test (Mice)
Dominant Lethal Test (Mice)

Long-term carcinogenicity studies in rats and mice have been completed. After daily oral dosing for up to 2 years, there is no evidence that ciprofloxacin had any carcinogenic or tumorigenic effects in these species.

Pregnancy—Pregnancy Category C: Reproduction studies have been performed in rats and mice at doses up to 6 times the usual daily human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ciprofloxacin. In rabbits, as with most antimicrobial agents, ciprofloxacin (30 and 100 mg/kg orally) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion. No teratogenicity was observed at either dose. After intravenous administration, at doses up to 20 mg/kg, no maternal toxicity was produced, and no embryotoxicity or teratogenicity was observed. There are, however, no adequate and well-controlled studies in pregnant women. SINCE CIPROFLOXACIN, LIKE OTHER DRUGS IN ITS CLASS, CAUSES ARTHROPATHY IN IMMATURE ANIMALS, IT SHOULD NOT BE USED IN PREGNANT WOMEN (SEE WARNINGS).

Nursing Mothers: It is not known whether ciprofloxacin is excreted in human milk; however, it is known that ciprofloxacin is excreted in the milk of lactating rats and that other drugs of this class are excreted in human milk. Because of this and because of the potential for serious adverse reactions from ciprofloxacin in nursing infants, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Patients under the age of 18 were not included in the clinical trials of ciprofloxacin because ciprofloxacin as well as other quinolones causes arthropathy in immature animals. Ciprofloxacin should not be used in children or adolescents (SEE WARNINGS).

ADVERSE REACTIONS

Ciprofloxacin is generally well tolerated. During clinical investigation, 2,799 patients received 2,868 courses of the drug. Adverse events that were considered likely to be drug related occurred in 7.3% of courses, possibly related in 9.2%, and remotely related in 3.0%. Ciprofloxacin was discontinued because of an adverse event in 3.5% of courses, primarily involving the gastrointestinal system (1.5%), skin (0.6%), and central nervous system (0.4%). Those events typical of quinolones are italicized.

The most frequently reported events, drug related or not, were *nausea* (5.2%), *diarrhea* (2.3%), *vomiting* (2.0%), *abdominal pain/discomfort* (1.7%), *headache* (1.2%), *restlessness* (1.1%), and *rash* (1.1%).

Additional events that occurred in less than 1% of ciprofloxacin courses are listed below.

GASTROINTESTINAL: *(See above)*, painful oral mucosa, oral candidiasis, dysphagia, intestinal perforation, gastrointestinal bleeding.

CENTRAL NERVOUS SYSTEM: *(See above)*, *dizziness*, *lightheadedness*, *insomnia*, *nightmares*, *hallucinations*, *manic reaction*, *irritability*, *tremor*, *ataxia*, *convulsive seizures*, *lethargy*, *drowsiness*, *weakness*, *malaise*, *anorexia*, *phobia*, *depersonalization*, *depression*, *paresthesia*.

SKIN/HYPERSENSITIVITY: *(See above)*, *pruritus*, *urticaria*, *photosensitivity*, *flushing*, *fever*, *chills*, *angioedema*, *edema of the face*, *neck*, *lips*, *conjunctivae or hands*, cutaneous candidiasis, hyperpigmentation, erythema nodosum.

Allergic reactions ranging from urticaria to anaphylactic reactions have been reported (SEE PRECAUTIONS).

SPECIAL SENSES: *blurred vision*, *disturbed vision (change in color perception*, *overbrightness of lights)*, *decreased visual acuity*, *diplopia*, *eye pain*, *tinnitus*, *hearing loss*, *bad taste*.

MUSCULOSKELETAL: *joint or back pain*, *joint stiffness*, achiness, neck or chest pain, flare-up of gout.

RENAL/UROGENITAL: *interstitial nephritis*, *nephritis*, *renal failure*, polyuria, urinary retention, urethral bleeding, vaginitis, acidosis.

CARDIOVASCULAR: palpitations, atrial flutter, ventricular ectopy, syncope, hypertension, angina pectoris, myocardial infarction, cardiopulmonary arrest, cerebral thrombosis.

RESPIRATORY: epistaxis, laryngeal or pulmonary edema, hiccough, hemoptysis, dyspnea, bronchospasm, pulmonary embolism.

Most of the adverse events reported were described as only mild or moderate in severity, abated soon after the drug was discontinued, and required no treatment.

In several instances, nausea, vomiting, tremor, restlessness, agitation, or palpitations were judged by investigators to be related to elevated plasma levels of theophylline possibly as a result of a drug interaction with ciprofloxacin.

Other adverse events reported in the postmarketing phase include anaphylactoid reactions, Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, hepatic necrosis, postural hypotension, possible exacerbation of myasthenia gravis, confusion, dysphasia, nystagmus, pseudomembranous colitis, dyspepsia, flatulence, and constipation. Also reported were agranulocytosis; elevation of serum triglycerides, serum cholesterol, blood glucose, serum potassium; prolongation of prothrombin time; albuminuria; candiduria, vaginal candidiasis; and renal calculi (SEE PRECAUTIONS).

Adverse Laboratory Changes: Changes in laboratory parameters listed as adverse events without regard to drug relationship:

Hepatic—Elevations of: ALT (SGPT) (1.9%), AST (SGOT) (1.7%), alkaline phosphatase (0.8%), LDH (0.4%), serum bilirubin (0.3%).

Cholestatic jaundice has been reported.

Hematologic—Eosinophilia (0.6%), leukopenia (0.4%), decreased blood platelets (0.1%), elevated blood platelets (0.1%), pancytopenia (0.1%).

Renal—Elevations of: Serum creatinine (1.1%), BUN (0.9%).

CRYSTALLURIA, CYLINDRURIA, AND HEMATURIA HAVE BEEN REPORTED.

Other changes occurring in less than 0.1% of courses were: Elevation of serum gammaglutamyl transferase, elevation of serum amylase, reduction in blood glucose, elevated uric acid, decrease in hemoglobin, anemia, bleeding diathesis, increase in blood monocytes, and leukocytosis.

OVERDOSAGE

Information on overdosage in humans is not available. In the event of acute overdosage, the stomach should be emptied by inducing vomiting or by gastric lavage. The patient should be carefully observed and given supportive treatment. Adequate hydration must be maintained. Only a small amount of ciprofloxacin (<10%) is removed from the body after hemodialysis or peritoneal dialysis.

DOSAGE AND ADMINISTRATION

The usual adult dosage for patients with urinary tract infections is 250 mg every 12 hours. For patients with complicated infections caused by organisms not highly susceptible, 500 mg may be administered every 12 hours.

Lower respiratory tract infections, skin and skin structure infections, and bone and joint infections may be treated with 500 mg every 12 hours. For more severe or complicated infections, a dosage of 750 mg may be given every 12 hours.

The recommended dosage for infectious diarrhea is 500 mg every 12 hours.

In patients with renal impairment, some modification of dosage is recommended (SEE DOSAGE AND ADMINISTRATION SECTION IN FULL PRESCRIBING INFORMATION).

HOW SUPPLIED

Cipro® (ciprofloxacin HCl/Miles) is available as tablets of 250 mg, 500 mg, and 750 mg in bottles of 50, and in Unit-Dose packages of 100 (SEE FULL PRESCRIBING INFORMATION FOR COMPLETE DESCRIPTION).

References: 1. Data on file, Miles Inc, Pharmaceutical Division. **2.** *Physicians' Desk Reference®*. 43rd ed. Oradell, NJ: Medical Economics Co Inc; 1989:891, 1376, 1441, 1486, 1724, 1779. **3.** Barry AL, et al. Antibacterial activities of ciprofloxacin, norfloxacin, oxolinic acid, cinoxacin, and nalidixic acid. *Antimicrob Agents Chemother*. 1984;25:633-637. **4.** Borner K, et al. Pharmacokinetics of ciprofloxacin in healthy volunteers after oral and intravenous administration. *Eur J Clin Microbiol*. 1986;5:179-186. **5.** Gombert ME, et al. Levels of ciprofloxacin in prostatic tissue of patients undergoing prostatectomy. *Rev Infect Dis*. 1988;10(suppl 1):S169. **6.** *Medi-Span® Hospital Formulary Pricing Guide*. June 1989:9,35.

***Achieves 97% favorable clinical response (resolution + improvement) of infections due to susceptible strains of indicated pathogens. See indicated organisms in prescribing information.**

For further information, contact the Miles Information Service:
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Total Parenteral Nutrition and Bowel Rest Modify the Metabolic Response to Endotoxin in Humans

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Intestinal mucosal atrophy, as induced by total parenteral nutrition (TPN) and/or prolonged bowel rest, is hypothesized to enhance bowel endotoxin (LPS) translocation and may alter host responses to infection. To examine the effect of TPN-induced bowel atrophy on the response to LPS, 12 healthy volunteers were randomized to receive either enteral feedings (ENT, n = 6) or seven days of TPN without oral intake (TPN, n = 6). Enteral or TPN feedings were terminated 12 hours before the study period when a constant dextrose infusion (50 mg/kg/hour) was initiated and continued throughout the subsequent study period. After placement of arterial, hepatic vein, and femoral vein catheters, metabolic parameters were determined before and for six hours after an intravenous *E. coli* LPS challenge (20 U/kg). Subsequent peak levels of arterial glucagon (ENT, 189 ± 39 pg/mL; TPN, 428 ± 48; $p < 0.01$), arterial epinephrine (ENT, 236 ± 52 pg/mL; TPN, 379 ± 49; $p < 0.05$) and hepatic venous cachectin/tumor necrosis factor (cachectin/TNF) (ENT, 250 ± 56 pg/mL; TPN, 479 ± 136; $p < 0.05$) were significantly higher in the TPN group than in the ENT group. The extremity efflux of lactate (ENT, −16 ± 4 μg/min-100cc tissue; TPN, −52 ± 13; t = 2 hours; $p < 0.05$) and of amino acids (ENT, −334 ± 77 nmol/min-100cc tissue; TPN, −884 ± 58; t = 4 hours; $p < 0.05$) were higher in the TPN subjects after the endotoxin challenge. Circulating C-reactive Protein (CRP) levels measured 24 hours postendotoxin were also significantly higher in the TPN subjects (ENT, 1.7 ± 0.2 mg/dL; TPN, 3.2 ± 0.3; $p < 0.01$). Hence the counter-regulatory hormone and splanchnic cytokine responses to LPS were enhanced after TPN and bowel rest. This is associated with a magnified acute-phase response, peripheral amino acid mobilization, and peripheral lactate production. Thus antecedent TPN may influence the metabolic alterations seen in infection and sepsis *via* both an exaggerated counter-regulatory hormone response as well as an enhanced systemic and splanchnic production of cytokines.

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THE LANDMARK WORK OF Dudrick et al.[1] introduced parenteral feedings as a means of nutritional supplementation for patients unable to receive nutrients by the enteral route. The use of this modality has favorably influenced the clinical outcome of many malnourished and injured patients. However recent evidence also suggests that significant differences in responses to infectious insult may exist between the enterally and parenterally fed states. In rodents total parenteral nutrition is associated with increased mortality to subsequent infection when compared with enterally fed animals.[2] In injured humans, total parenteral nutrition is associated with an exaggerated acute-phase protein response when compared to enterally fed patients[3] and may be associated with increased septic complications.[4] Among the postulated mechanisms for such differences in postinjury response related to the route of feeding is that enteral nutrition exerts trophic influences on bowel structural and functional integrity.[5] As a consequence lack of enteral feeding is postulated to predispose the patient to amplification of injury-induced metabolic and immunologic responses.

The splanchnic organs are vital in normal homeostasis as well as in the host responses to injury. Not only is the splanchnic bed a site of essential metabolic activity,[6] the gastrointestinal tract also functions as a barrier to the indigenous luminal bacteria and toxins.[7] Bowel rest and parenteral nutrition are known to produce alterations in gastrointestinal integrity, leading to mucosal atrophy[8] and, in some experimental models, increased translocation of luminal bacteria across the mucosal barrier.[9] The metabolic consequences of these bowel-rest-induced alterations

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in intestinal barrier function are largely unknown. Although it is postulated that antecedent loss of bowel functional integrity influences the response to injury, the multifactorial nature of clinical disease makes assessment of this hypothesis difficult in injured patients.

Endotoxin (lipopolysaccharide, LPS) triggers many of the responses associated with injury and infection. This bacterial cell wall component clearly elicits hemodynamic and immune alterations[10] associated with infection. Endotoxin injections also produce increased intestinal permeability[11] and bacterial translocation.[12] Furthermore a single bolus of endotoxin can elicit release of endogenous mediators[13,14] and can acutely induce many of the whole-body and splanchnic metabolic alterations associated with injury.[15,16]

To assess whether antecedent bowel rest, independent of overt malnutrition, would alter the host response to injury, endotoxin was administered to volunteers who had been maintained on 1 week of weight-stable parenteral feedings. The consequent mediator and metabolic responses were compared with a previously described population of volunteers[15] who received the same endotoxin injection but without antecedent bowel rest.

Materials and Methods

Subjects

Twelve subjects aged 26 ± 1 years and within 10% of ideal body weight for age, sex, and height (Metropolitan Life Table, 1983) were admitted to the Adult Clinical Research Center (CRC) of the New York Hospital-Cornell Medical Center (NYH-CMC) after screening by complete physical exam, blood count, serum biochemistries, electrocardiogram, and chest roentgenogram. The study was approved by the Institutional Review Board of the NYH-CMC and informed written consent was obtained from each subject before enrollment into the study.

Study Protocol

From the time of admission until discharge all subjects were allowed to ambulate within the ward but were restricted from any other physical activity. Subjects were weighed daily at 6:00 AM after voiding, and oral temperatures were monitored every 8 hours.

As previously described[15] the enterally fed subjects (ENT) (n = 6) were provided a defined formula diet (Sustacal, Mead-Johnson, Evansville, Indiana) in six equal daily portions. This diet was provided at 1.2 times the measured resting energy expenditure (REE). Oral feedings were discontinued at 8:00 PM the day before the endotoxin challenge when an intravenous infusion of 5% dextrose (50 mg/kg/hour) was begun. This hypocaloric dextrose infusion was designed to simulate the clinical situation of dextrose infusions in hospitalized patients, and was continued throughout the study period.

A percutaneous catheter was inserted into the antecubital veins of subjects in the second group (TPN) (n = 6) and advanced into the superior vena cava (placement confirmed by chest roentgenography). These subjects then received intravenous feedings for seven days with a commercially available amino acid source (Aminosyn-5%) and 100% of the nonprotein calories as D-glucose. The nutrients provided were 29 ± 2 nonprotein kcal/kg/day, and 0.29 ± 0.02 gN/kg/day. This feeding regimen was isocaloric to the enteral feedings of group 1. Appropriate electrolytes, trace minerals, and vitamins were added. At 8:00 PM the day before the endotoxin challenge, TPN was discontinued and a hypocaloric dextrose infusion was begun (50 mg/kg/min) and continued throughout the study period.

At 9:00 AM on the study days, a transcutaneous hepatic vein catheter was inserted under fluoroscopic guidance through a femoral site to allow blood sampling for cytokine levels. A retrograde femoral venous catheter and a radial arterial catheter were also placed. The position of the hepatic venous catheter in the right hepatic vein was verified by contrast radiography. Blood pressure, heart rate, rectal temperature, and respiratory rates were continuously monitored. After baseline metabolic rate measurements and blood samplings for substrates, hormones, and cytokines, each subject received an intravenous injection of National Reference Bacterial Endotoxin (Lot EC-5, 20 Units/kg over 5 minutes). The endotoxin was prepared from *Escherichia coli* 0113 and was provided by Dr. H. D. Hochstein (Office of Biologics, Food and Drug Administration).[17] Repeated measurements for metabolic rate, substrate concentrations, organ substrate flux, hormone levels, and cytokine levels were performed over the next six hours as outlined below.

Extremity Blood Flow

Extremity blood flow was performed before and after each blood sampling for substrate concentrations using electrocapacitance plethysmography.[18]

Hormones

Arterial specimens were used for all determinations of hormone levels. Plasma for glucagon was collected with EDTA and aprotinin before analysis by radioimmunoassay.[19] Epinephrine levels were determined by radioenzymatic assays[20] on specimens collected in tubes containing EGTA and reduced glutathione. Insulin[21] was measured by radioimmunoassay on specimens collected in tubes containing EDTA.

Cachectin/TNF Levels

Simultaneous arterial and hepatic venous blood samples at baseline (BL), and at 15-minute intervals after the

TABLE 1. *Temperature (Temp), Heart Rate (HR), and Mean Blood Pressure (BP) Before and After Endotoxin Challenge*

	Temp		HR		BP	
Time (minutes)	ENT	TPN	ENT	TPN	ENT	TPN
−60	36.4 ± 0.1	36.9 ± 0.1†	58 ± 5	74 ± 2†	83 ± 6	77 ± 6
0	36.5 ± 0.1	37.0 ± 0.1†	55 ± 3	73 ± 2†	84 ± 4	78 ± 6
60	36.7 ± 0.1	37.3 ± 0.1	62 ± 5	80 ± 6†	87 ± 5	76 ± 9
120	37.5 ± 0.1*	38.8 ± 0.2*†	77 ± 7*	98 ± 4*†	79 ± 4	68 ± 6
180	38.2 ± 0.1*	39.1 ± 0.1*†	78 ± 8*	97 ± 3*†	76 ± 3	63 ± 7
240	38.2 ± 0.1*	38.7 ± 0.1*†	86 ± 6*	103 ± 6*†	81 ± 6	65 ± 5
300	38.2 ± 0.2*	38.5 ± 0.2*	80 ± 8*	100 ± 4*†	80 ± 6	67 ± 7
360	38.0 ± 0.1*	38.4 ± 0.2*	76 ± 6*	103 ± 2*†	85 ± 6	66 ± 4

Values are means ± SE. *$p < 0.05$ *vs.* $t = 0$; †$p < 0.05$ ENT *vs.* TPN. Measurement at $t = 0$ was made immediately before the injection of endotoxin.

ENT, enteral feeding before treatment; TPN, total parenteral nutrition before treatment.

endotoxin challenge were collected in heparinized tubes. These were immediately centrifuged at 4 C to separate the plasma, which was stored at −70 C until determination of cachectin/TNF level by a previously described ELISA.[13] The lower limit of detection for this ELISA is 34 pg/mL.

Substrate Concentrations

Plasma glucose concentrations were determined using an automated glucose analyzer (Model 23A, Yellow Springs Instrument Co., Yellow Springs, OH) using the glucose oxidase reaction.[22] Whole blood was immediately precipitated in ice-cold perchloric acid and stored at −70 C until analysis by an enzymatic assay for lactate concentration.[23] Plasma amino acids were determined by anion exchange chromatography on a Perkin-Elmer HPLC system (Perkin-Elmer, Norwalk, CT) using a three-buffer lithium system with norleucine as an internal standard[24] and a Pickering post-column ninhydrin detection system (Pickering Laboratories, Mountain View, CA).

Substrate Flux

Arterial and femoral venous samples for substrate analysis were drawn simultaneously. Extremity substrate flux was calculated as the product of the arterial–venous difference in substrate concentration and the extremity of blood flow.[25] A positive value represents a relative uptake across the extremity, whereas a negative flux indicates an efflux.

C-Reactive Protein Assay

Quantitation of the circulating C-reactive protein (CRP) levels was performed by standard radial immunodiffusion (Behring Diagnostics, LaJolla, CA). Plasma specimens from admission, immediately before, six hours after the endotoxin challenge, as well as a specimen 24 hours after the endotoxin challenge were measured. The lower limit of detection of this assay is 0.5 mg/dL.

Statistical Analysis

All data are expressed as means ± S.E.M. Standard paired Student's t tests were used for single comparisons. ANOVA and Least Significant Difference tests, where appropriate, were used to identify statistical significance for multiple comparisons. Nonparametric statistical analysis was performed using the Wilcoxin matched pairs signed-rank test; $p < 0.05$ was considered statistically significant.

Results

Body Weights and Vital Signs

The TPN regimen used in the current study maintained the body weight of the study subjects (before TPN, 78 ± 7 kg; after TPN, 78 ± 7 kg). Pyrogenic responses were noted after the endotoxin challenge in both feeding conditions (Table 1). The peak change in temperature (ENT, 1.8 ± 0.1 C; TPN, 2.2 ± 0.1 C; $p < 0.05$ by Wilcoxin) was greater in magnitude in subjects pretreated with 1 week of total parenteral nutrition. The heart rate response to endotoxin was also greater in the TPN group (Table 1). Neither group exhibited significant change in mean blood pressure in response to endotoxin.

Hormonal Response

Peak circulating epinephrine and glucagon responses were noted 120 minutes after the endotoxin challenge (Fig. 1). This peak response was significantly greater in the TPN group as compared to the ENT group (epinephrine: ENT, 236 ± 52 pg/mL; TPN, 379 ± 49 pg/mL; $p < 0.05$) (glucagon: ENT, 189 ± 39 pg/mL; TPN, 428 ± 48 pg/mL; $p < 0.01$). No change of circulating insulin levels was noted during the study in either group.

Arterial cachectin/TNF levels were detectable within 60 minutes of the endotoxin challenge (Fig. 2). Hepatic venous levels were consistently higher than arterial levels whenever this protein was detected in the circulation.

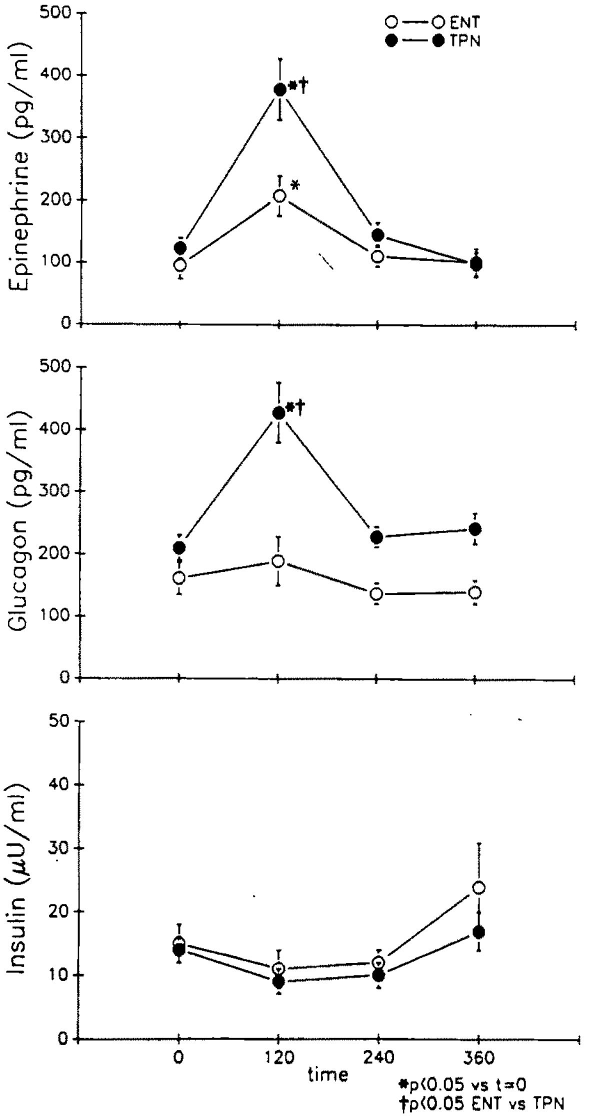

FIG. 1. Hormonal response to endotoxin. Epinephrine, glucagon, and insulin levels in arterial blood before (t = 0) and after the endotoxin bolus. Subjects were studied 12 hours after the cessation of either enteral feedings (ENT) or total parenteral nutrition (TPN). All subjects received 5% dextrose (50mg/kg/hour) at the time of the study. Time is expressed in minutes.

Moreover circulating cachectin/TNF levels from both the arterial and the hepatic venous sites were significantly higher at all detectable time points in the TPN group than in the ENT group (Arterial peak: ENT, 131 ± 48 pg/mL; TPN, 292 ± 74 pg/mL; $p < 0.05$) (Hepatic venous peak: ENT, 201 ± 60 pg/mL; TPN, 479 ± 136 pg/mL; $p < 0.05$) (Fig. 2).

Carbohydrate Metabolism

In the ENT group a progressive hyperglycemia was observed within 120 minutes after the endotoxin challenge, accompanied by an increased uptake of glucose in the lower extremity by 240 minutes (Fig. 3). By contrast subjects in the TPN group had neither changes in circulating glucose levels nor alterations in extremity glucose balance in response to endotoxin. However the peripheral production of lactate was significantly increased in the TPN subjects compared to the ENT subjects (Fig. 3). This was consequently accompanied by significant increases in circulating levels of this three-carbon substrate in the TPN subjects.

Amino Acid Metabolism

Hypoaminoacidemia developed within 120 minutes after endotoxin challenge in both study groups (Fig. 4). This decrease in circulating amino acids involved essential amino acids as well as the prominent nitrogen carriers alanine and glutamine. Significant alterations in extremity handling of amino acids were also noted between the two groups. Total amino acid efflux from the extremity doubled at 240 minutes ($p < 0.01$ *vs.* BL) after the endotoxin challenge in the group subjected to TPN. Increases in alanine and glutamine efflux from the extremity in this group of subjects represented more than one half of this increase in total extremity amino acid efflux (Fig. 4).

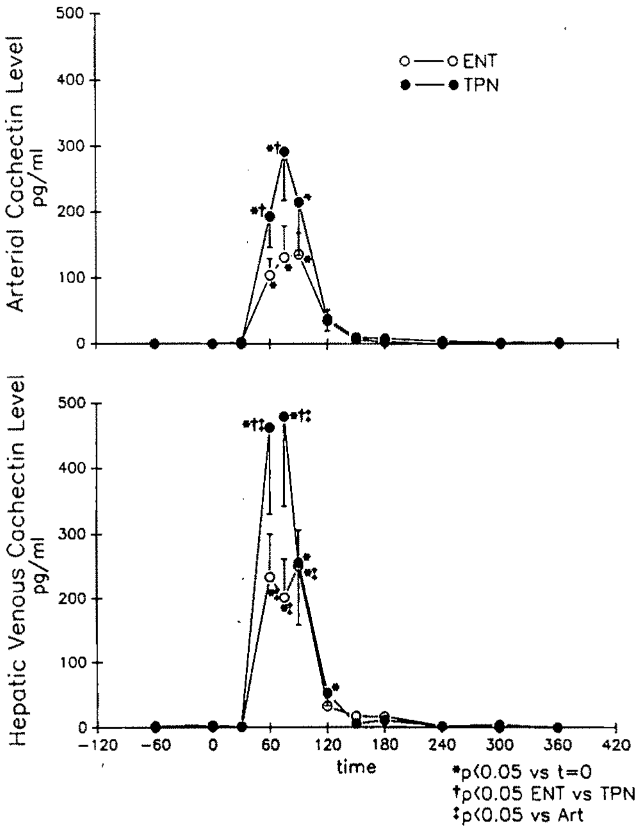

FIG. 2. Cachectin/TNF levels. Cachectin levels in the arterial and hepatic venous blood of volunteers before (t = 0) and after the endotoxin injection. Subjects received either enteral feedings (ENT) or parenteral feedings (TPN) as pretreatments.

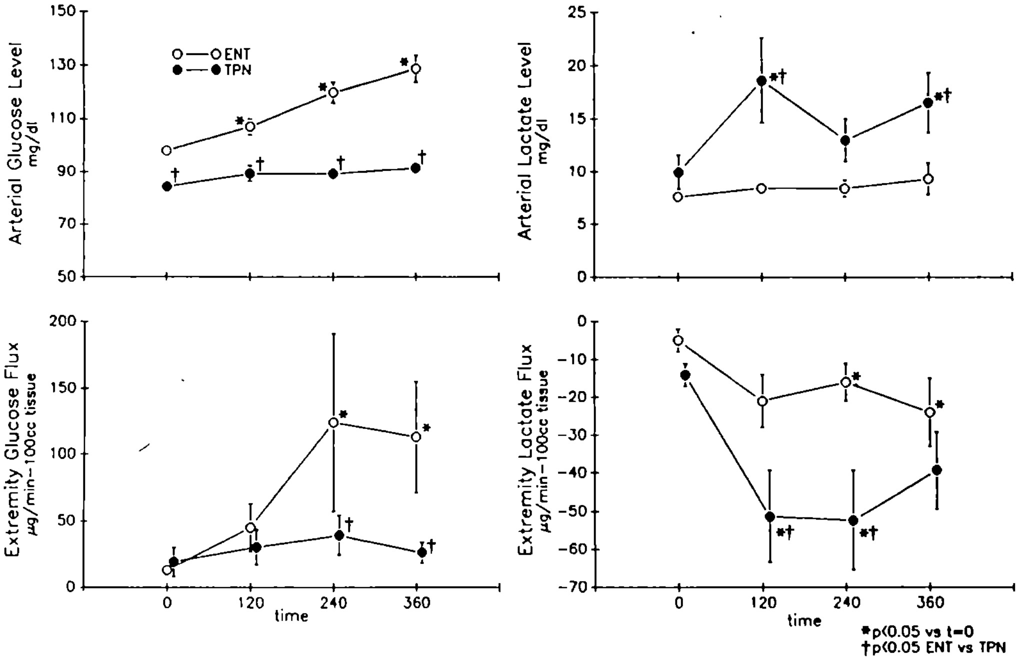

FIG. 3. Glucose and lactate responses to endotoxin. Arterial levels, as well as extremity flux of these substrates, are illustrated. A positive flux indicates uptake of substrate by the extremity, while a negative flux indicates an efflux. Subjects were studied 12 hours after the cessation of either enteral feedings (ENT) or total parenteral nutrition (TPN). All subjects received 5% dextrose (50mg/kg/hour) at the time of the study.

C-Reactive Protein

No circulating CRP levels were detected in either group on admission (Fig. 5). Six hours after the endotoxin injection, detectable levels of CRP were noted in the TPN group, while levels in the ENT group were still below detection. Twenty-four hours after the endotoxin injection, CRP levels in the TPN group remained significantly higher ($p < 0.01$) than in the ENT group.

Discussion

The route of feeding has been hypothesized to exert an influence on the course of clinical disease. More specifically enteral feedings are believed to be of particular benefit in the setting of injury[2,4] as trophic influences related to enteral feeding are believed to be necessary for maintenance of intestinal mucosal integrity.[8] In addition total parenteral nutrition and bowel rest in experimental models are associated with decreased secretion of intestinal IgA[26] and increased translocation of bacteria across the mucosal barrier[9] when compared to enteral feedings. Theoretically enteral nutrients may not only preserve the barrier function of the intestinal tract to indigenous luminal bacteria and other foreign antigens but also modulate splanchnic reticuloendothelial cell function in the process.

The current study examines the hormonal and metabolic background of enterally and parenterally fed subjects and compares the responses of these subjects to endotoxemic injury. Although the circulating hormonal and metabolic milieu in the nonstressed, basal state were equivalent between these groups, endotoxemia was accompanied by an enhanced endogenous mediator, as well as by peripheral tissue metabolic response in subjects who received previous TPN. Hence withdrawal of enteral feedings, even in the absence of overt antecedent malnutrition, was associated with alterations in metabolic response to controlled endotoxemic injury.

In addition to important nutrient absorptive and metabolic functions, the gastrointestinal tract is an immunologically important organ in which vital interactions with foreign antigens occur. The hepatic Kupffer cells are the largest pool of tissue macrophages[27] and the gut-associated lymphoid tissues comprise 50% of the body lymphoid tissues.[28] Secretory products of stimulated splanchnic lymphocytes and macrophages, such as cachectin/TNF, interleukin-1, and interleukin-6 are known to be important determinants not only of the immune and hemodynamic responses to injury but also the metabolic responses to injury.[14,29] The teleologically advantageous site of splanchnic immune cells permits their secretory proteins to exert rapid paracrine influences on neighboring splanchnic cells that perform important metabolic processes, such as gluconeogenesis and hepatic protein synthesis. In addition these products of activated lymphocytes and monocytes may be released into the systemic circulation where they may exert endocrine effects as well.

The gastrointestinal tract is also a reservoir of bacteria, bacterial products, and ingested particles. Alterations in the intestinal flora or permeability may have immune and metabolic consequences. This luminal pool of foreign antigens is necessary for normal intestinal lymphoid tissue[27] and mucosal cell renewal,[30] as well as intact systemic responses to infection.[31] The indigenous bacteria are also

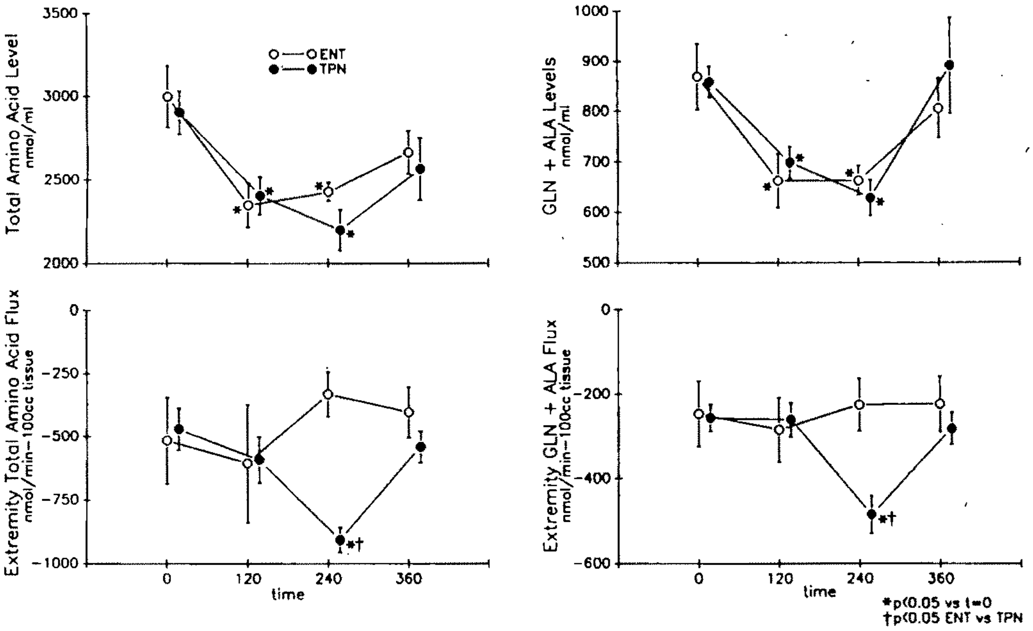

FIG. 4. Amino acid responses to endotoxin. Arterial levels, as well as extremity flux of total amino acids, or the sum of glutamine (GLN) and alanine (ALA), are shown. A positive flux indicates uptake of substrate by the extremity, while a negative flux indicates an efflux. Subjects were studied 12 hours after the cessation of either enteral feedings (ENT) or total parenteral nutrition (TPN). All subjects received 5% dextrose (50mg/kg/hour) at the time of the study.

believed to be a source of systemic bacteremia and endotoxemia,[28] particularly during injury or stress conditions. Bowel rest and parenteral nutrition are known to produce increased translocation of bacteria to the intestinal lymphoid tissue in some animal models.[9] Bowel rest is also known to produce overgrowth of bacteria in the intestinal lumen.[32] Altering the gastrointestinal flora by experimental bacterial overgrowth enhances responsiveness of hepatic Kupffer cells.[27] We therefore hypothesized that TPN and previous bowel rest would result in increased splanchnic and systemic reticuloendothelial cell responsiveness to subsequent injury. The enhanced arterial and hepatic venous cachectin response in the parenterally fed subjects is consistent with an increased reticuloendothelial system responsiveness in these subjects.

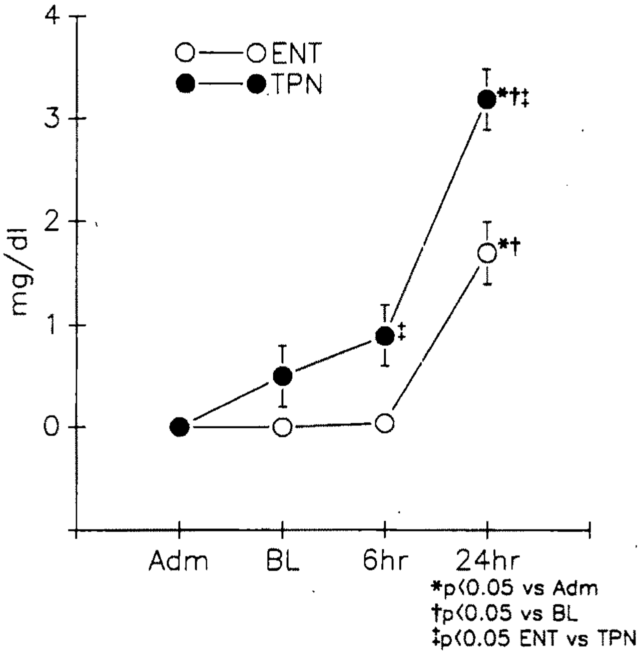

FIG. 5. C-reactive protein response. The C-reactive protein concentration in the arterial blood on admission (Adm), immediately before (BL), six hours, and 24 hours after endotoxin challenge. Levels below the detection limit (0.5 mg/dL) are illustrated as 0.

A differential response was also noted in other components of the endogenous mediator cascade, including glucagon and epinephrine. In endotoxemic injury, cachectin/TNF is triggered early in the cascade of host mediators.[29] We have previously observed that this cytokine induces the release of the counter-regulatory hormones glucagon and epinephrine.[33] Hence it is not surprising that a differential cachectin/TNF response is also associated with a dose response in counter-regulatory hormone levels.

The parenterally fed subjects also exhibited a different metabolic response to endotoxin than the enterally fed subjects. Lactic acidemia, hypoaminoacidemia, increased peripheral production of lactate, and increased peripheral release of amino acids are predictable responses to injury and endotoxemia.[6] The lactate response in experimental endotoxemia is dependent on the dose of administered endotoxin[34] and is initiated, in part, by cachectin/TNF[33,35] and epinephrine.[36] The peripheral mobilization of amino acids seen with injury can also be reproduced by infusions of cachectin/TNF.[37,38] This efflux of amino acids from the periphery seen in response to cachectin/TNF is also dose dependent.[37] C-reactive protein is an acute-phase protein produced by hepatocytes that is used as an indication of the severity of injury.[39] Synthesis of this protein is also triggered by monocyte-derived mediators.[40] Thus several of the metabolic responses distinguishing the TPN group from the ENT group can be explained in part by the exaggerated humoral-cytokine responses to endotoxin in the TPN subjects.

We can only speculate on the mechanism of this heightened mediator and metabolic response to endotoxin in subjects with previous bowel rest and TPN. Data from animal studies demonstrate that bacteria can be cultured from the intestinal lymphatics during bowel rest and parenteral nutrition.[9] *In vitro* data further demonstrate the potentiating effects of IFN-gamma,[41] IL-2,[42] IL-4,[43] and other lymphokines[44] on macrophage responsiveness to foreign antigens. Removal of splanchnic lymphoid tissue by splenectomy is associated with suppressed Kupffer cell function.[45] Thus increased release of lymphokines by intestinal lymphoid tissue in response to TPN-induced exposure to bacteria or other luminal antigens is a possible mechanism in the exaggerated response to endotoxin. Other factors, such as components of the complement cascade, may also increase the responsiveness of macrophages.[46] Intestinal epithelium and macrophages in the bowel wall can produce complement.[46] Activation of these cells may trigger the release of complement, which stimulates the reticuloendothelial system. Furthermore certain bacterial cell wall components, such as peptidoglycans, are potential adjuvants to the effects of endotoxin.[47] Release of such compounds during bacterial degradation may also contribute to the enhanced responsiveness to endotoxin. Finally previous bowel rest and mucosal atrophy may enhance exposure of the host to luminal endotoxin. Hence despite the administration of an equivalent intravenous LPS dose to both groups, previous TPN and bowel rest may enhance host uptake of luminal endotoxin and thereby increase the effective regional or systemic endotoxin level. It is difficult to distinguish among these and other mechanisms in a human *in vivo* study. Furthermore it is likely that the current findings are multifactorial. These findings nevertheless encourage further investigation of the mechanisms of altered susceptibility to endotoxin with parenteral feedings.

It is not surprising that numerous studies using nonstressed subjects[48] or stable patients[49,50] have been unable to distinguish between enteral and parenteral nutrition by measures of weight gain and nitrogen balance. In nonstressed individuals and patients beyond the early phase of injury, these basic metabolic parameters are likely to be more dependent on the caloric and nitrogen content of the administered feedings than on the route of feedings. These previous studies therefore compared the nutrient-absorptive capacity of the gastrointestinal tract to direct intravenous infusion of nutrients. Baseline hormonal and metabolic data from the present study also demonstrate that nonstressed subjects treated with previous TPN and bowel rest are indistinguishable from enterally treated subjects. However even the relatively small stress of the current endotoxin dose produces significantly different responses between these groups and demonstrates the importance of considering stress-related responses in evaluation of nutritional support modalities.

Immune and metabolic processes closely interact not only in maintaining normal homeostasis but also in the responses to injury. The gastrointestinal tract is an important site of such interactions. Data from the current study suggest that bowel rest produces alterations in host resistance to injury independent of malnutrition. Although the mechanisms of these alterations require further investigation, these results suggest that the route of feeding indeed affects injury and disease.

Acknowledgments

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DISCUSSION

DR. STANLEY M. LEVENSON (Bronx, New York): I haven't had the opportunity of reading Dr. Lowry's paper, and I am sure that there is much additional information in the manuscript that is important in trying to interpret the findings and to speculate as to the mechanism(s) of the striking observations he has reported. One might conclude from the data presented that a current parenteral nutrition regimen commonly used clinically may not be optimal. We don't know what are the optimal parenteral regimens. I have mentioned regimens because we know enough to realize that a number of regimens will be needed for varying clinical situations. We know much more about oral diets than parenteral ones. I asked Dr. Lowry this morning what the enteral feeding used in his study was; it was the commercial preparation Sustacal (Mead Johnson Enteral Nutritionals, Evanville, IN), which contains milk-derived protein, not an amino acid enteral preparation.

We know from the work of Wooley at the Rockefeller many years ago that, at least for bacteria, there are certain peptide(s) (which he called strepogenin) which stimulate growth to a greater extent than individual amino acids. We don't know at this time whether there are special nutritional attributes of peptides for patients. Peptides are not included in the current commercially available parenteral regimes but this matter is under active investigation. We know that small peptides are absorbed from the GI tract when protein is given and that their absorption is generally faster than that of amino acids.

What one would like to do experimentally (and clinically) is to provide a parenteral nutrition regimen(s) in which gut atrophy did not occur, compare such regimen(s) with enteral regimen(s) that also prevented gut atrophy, and determine whether metabolic, physiologic, and immunologic differences would be found between those parenterally fed and those enterally fed.

I think that Dr. Lowry's study is a good start at looking at some very important questions. I think that as time goes on, and certainly Dr. Wilmore's data and those of other investigators suggest that, we will be modifying the composition of the parenteral nutrition regimens we use for our patients.

DR. LEWIS MATTHEW FLINT (Buffalo, New York): I would just like to ask if in the circumstances of this experiment, are there any evidences of changes in circulating counts of platelets or polymorphonuclear leucocytes, and is there evidence of sequestration of these elements, for instance, in the lung?

DR. JOHN A. MANNICK (Boston, Massachusetts): I cannot let this excellent paper go by without a word of congratulation to the authors, and I would just like to ask Dr. Lowry two questions.

Regarding Dr. Levenson's questions, Dr. Lowry, was there any glutamine in your parenteral nutrition solution? And second do you have any information about the effects of these high-level burst TNF secretions that you have seen on the function of either circulating lymphocytes or monocytes?

DR. S. F. LOWRY (Closing discussion): Dr. Levenson has emphasized the importance of peptides, and the extent to which they are absorbed and used by the gastrointestinal tract. The potential for altering parenteral feeding regimens with peptides is being investigated extensively around the world. Whether the intravenous administration of peptides will prove to be metabolically equivalent to those provided enterally remains to be seen. There are a number of biochemical problems referable to the degradation sites for dipeptides that may exclude their intravenous use, and they are currently costly.

Dr. Flint has asked whether there are changes in circulating neutrophils and any evidence of sequestration. With respect to the latter, there was no evidence of sequestration. The subjects did not demonstrate any clinical pulmonary changes or alterations in arterial blood gases. In addition, there has been no evidence of pulmonary parenchymal change after endotoxin administration in the few patients in whom we have checked chest x-rays.

There were, at least transiently, significant changes in the circulating white cell populations, and this is an area of active investigation by members of our department. As alluded to by Dr. Mannick, we believe that periodic bursts of circulating tumor necrosis factor and other cytokines are probably quite important but not necessarily in the classical endocrine sense. From our own data, which is in press, we are unable to document that circulating levels of this cytokine are consistently observed in critically ill patients, where such a response might be anticipated. While this has seemingly been a problem relating circulating levels to systemic or tissue responses, we have recently identified a cell-associated form of tumor necrosis factor that appears on tissue-fixed macrophages as well as circulating monocytes. This is probably a major effector form of tumor necrosis factor. As a consequence what we see in the circulation is only part of the story and may represent amplification of cytokine production at the tissue level. Hence circulating levels may be only partly reflective of the ligand activity within tissue sites.

Finally, Dr. Mannick asked whether there was any glutamine in the parenteral regimen, and the answer to that is negative. While the current literature supports the role of glutamine as a cytoproliferative agent, by and large such observations have not been translated into functional results such as improved survival to bacterial challenge. Glutamine is not routinely included in current parenteral feeding regimens and, I believe, we have much to learn about the beneficial as well as potential toxic effects of glutamine before conscionably advocating its addition to parenteral feeding solutions.

Relationship of a Satisfactory Outcome to Normalization of Delayed Gastric Emptying After Nissen Fundoplication

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Delayed gastric emptying in patients with gastroesophageal reflux disease may be due to an incompetent distal esophageal sphincter and/or a gastric abnormality. To determine the influence of the Nissen fundoplication on gastric emptying we studied the rate of gastric emptying before and after operation in 25 patients with proved gastroesophageal reflux disease. Nine patients had no gastric pathology, 9 had gastric acid hypersecretion, 5 had gastritis, and 2 had evidence of significant duodenogastric reflux. All were treated by Nissen fundoplication. Those with gastric acid hypersecretion also had a proximal gastric vagotomy (PGV) and the two patients with pathologic duodenogastric reflux were treated by a bile diversion procedure. We found that in gastroesophageal reflux disease with associated gastric pathology there was a higher prevalence of delayed gastric emptying before operation than in patients without gastric pathology. Nissen fundoplication was associated with speeding of gastric emptying in patients with or without gastric pathology. Proximal gastric vagotomy performed in association with Nissen fundoplication augmented the speeding of gastric emptying, which was advantageous in most cases but detrimental in two. Every patient in whom gastric emptying was not normalized had postoperative symptoms. Only two of 20 patients with normal postoperative gastric emptying had postoperative symptoms. Both patients had preexisting gastric pathology. Based on these findings, the side effects associated with Nissen fundoplication are due to the failure to normalize gastric emptying rather than the operation.

TWO THIRDS OF PATIENTS with foregut symptoms such as heartburn, regurgitation, dysphagia, cough, chest pain, or epigastric pain have increased esophageal exposure to gastric juice and one half have abnormal gastric emptying. When these are present they occur separately or together so that 41% of patients have increased esophageal acid exposure alone, 19% have abnormal gastric emptying alone, and 40% have both.[1] This suggests that an incompetent distal esophageal sphincter and/or gastric emptying abnormalities are common mechanisms that could account for these symptoms. The Nissen fundoplication procedure is reported to give relief from heartburn and regurgitation in 91% of patients followed for 10 years.[2] Despite the success in controlling reflux, some patients have persistent or new postoperative symptoms such as epigastric pain, nausea, bloating, diarrhea, and dumping.[3] These may result from persistent or induced alterations in gastric emptying. The abnormal gastric emptying associated with gastritis, gastric acid hypersecretion, and duodenogastric reflux, which may be present before operation, is not specifically addressed by fundoplication. Consequently it may persist after operation. Furthermore fundoplication, in addition to controlling reflux, speeds gastric emptying.[4] The resulting combination of these effects on gastric emptying may be beneficial or detrimental. It was the aim of this study to correlate changes in the rate of gastric emptying with the outcome after fundoplication in patients with and without evidence of gastric pathology.

Study Population and Methods

Normal Controls

Gastric emptying studies were performed on normal volunteers who did not have a history of foregut symptoms and who had normal upper gastrointestinal barium studies, esophageal manometry, and 24-hour esophageal pH monitoring. The details of this group have been described previously.[1]

Patients

The study population consisted of 25 symptomatic patients, with documented gastroesophageal reflux disease

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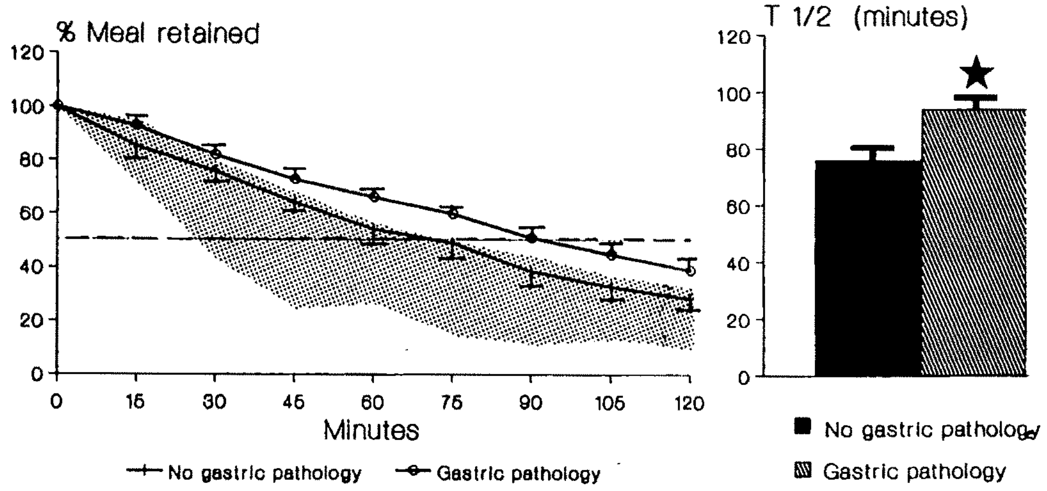


FIG. 1. Preoperative gastric emptying in 16 patients with gastric pathology (open circles) and in nine patients without gastric pathology (solid line). The shaded area represents the 10th to 90th percentiles of normal. The mean T½ is illustrated in the bar graph and shows delayed gastric emptying in patients with gastric pathology (* = $p < 0.05$).

on 24-hour esophageal pH monitoring in 23, and standard acid reflux test in two patients who were achlorhydric. All but three patients had a defective cardia on preoperative motility testing.[5] There were 13 men and 12 women, with a mean age of 53.4 years (range, 31 to 71 years). A detailed history was taken from all patients before operation and a long-term follow-up interview, either in person or by telephone, took place a median of 18 months after fundoplication (range, 5 to 48 months). In both a standard questionnaire was used by an independent observer to record the presence of foregut symptoms including heartburn, regurgitation, dysphagia, epigastric discomfort, nausea, vomiting, chest pain, and persistent cough. Patients were also asked for their own assessment of the procedure.

Before surgery all patients underwent fiberoptic endoscopy and biopsy, esophageal manometry, 24-hour esophageal pH measurement, and a gastric emptying test as described previously.[5,6,1] Acid secretory studies were performed in 19 patients with a history of ulcer disease. Hypersecretion was defined as basal acid output (BAO) > 5 mmol/h and maximum acid output (MAO) > 30 mmol/h.[7] Nine patients had preoperative documented gastroesophageal reflux without evidence of gastritis, gastric acid hypersecretion, or pathologic duodenogastric reflux on 24-hour gastric pH and hepatoiminodiacetic acid (HIDA) testing.[7,8] Sixteen patients had documented gastroesophageal reflux with gastric pathology (gastritis alone in 5 patients, gastric acid hypersecretion in 9, and duodenogastric reflux in 2). All patients had a Nissen fundoplication. The nine patients with gastric acid hypersecretion underwent fundoplication and a PGV. The two patients with duodenogastric reflux underwent Nissen fundoplication and a bile diversion procedure, the duodenal switch.[9] Gastric emptying studies were repeated a median of 12 months after surgery (range, 1 to 35 months).

Gastric Emptying Studies

A meal was given in the fasting state and consisted of 56 g of instant oatmeal, 6 g of sugar, and 175 mL of water, mixed with 500 μCi Tc-99m sulphur colloid and followed

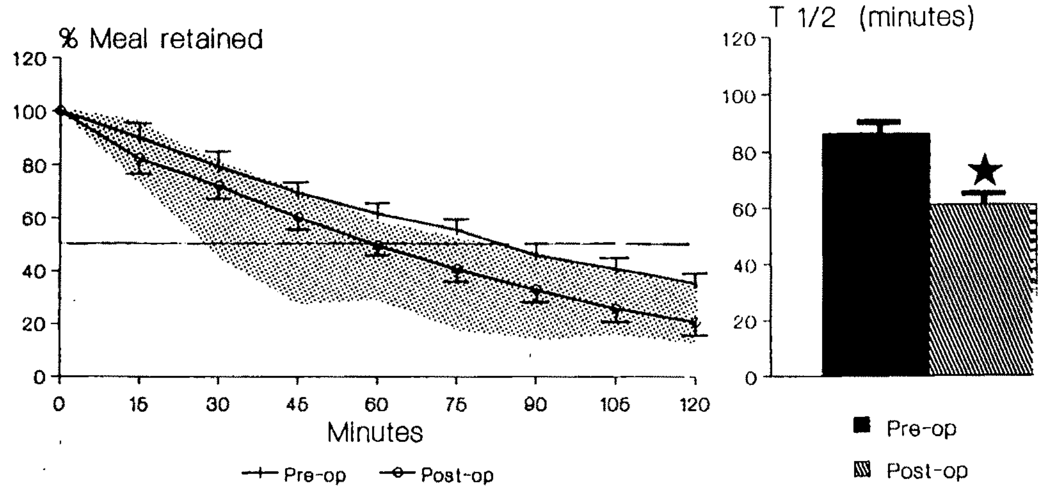


FIG. 2. Preoperative *versus* postoperative gastric emptying in all 25 patients. The shaded area represents the 10th to 90th percentiles of normal. The mean T½ is illustrated in the bar graph and shows the speeding of postoperative emptying (* = $p < 0.05$).

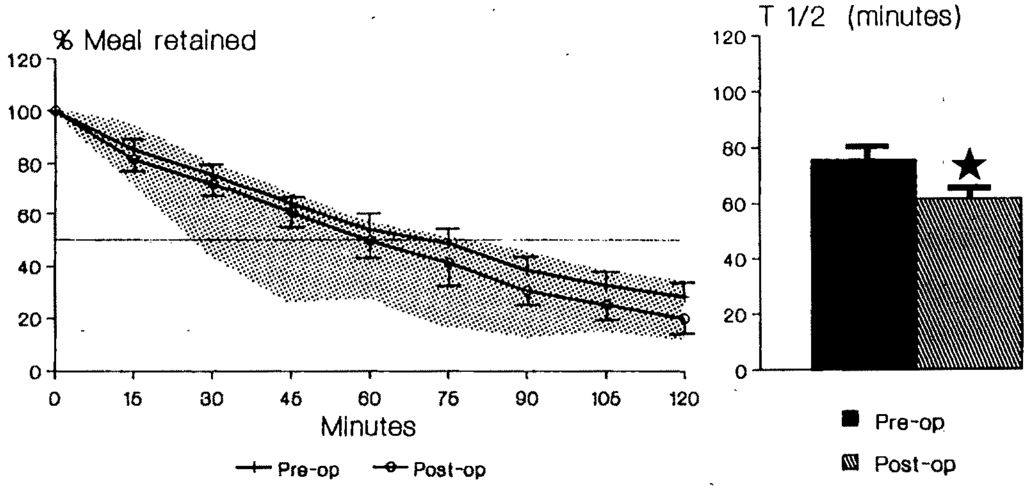


FIG. 3. Preoperative *versus* postoperative gastric emptying in nine patients without gastric pathology. The shaded area represents the 10th to 90th percentiles of normal. The mean T½ is illustrated in the bar graph and shows that fundoplication in the absence of gastric pathology increases gastric emptying (* = $p = 0.05$).

by 240 mL of 2% milk. (Total protein, 18 g; carbohydrate, 28 g; fat, 9 g; 380 KCal).

Gamma camera images were obtained in the upright, anterior, and posterior projections for 40 seconds at the completion of the meal and every 15 minutes for 90 to 120 minutes.[1] The geometric mean of the anterior and posterior counts per minute for the gastric region of interest were adjusted for decay of the isotope and expressed as a percentage of the initial counts over the stomach area.[10] To identify rapid or delayed emptying, either the emptying curve or T½ was used as an end point. Using the former a patient was considered to have abnormal emptying if his curve at 90 minutes was outside the 10th to 90th percentile range of normals and remained so at 105 and 120 minutes. Using the latter the patient was considered to have abnormal emptying if the T½ was outside the 5th and 95th percentile of normals.

Operative Technique

The Nissen fundoplication was performed as previously described using a 1-cm fundic wrap over a size 60 French bougie.[2] Particular care was taken to identify and preserve both vagal nerve trunks.

Statistical Methods

Nonparametric tests for paired and unpaired data were used to compare the T½ before and after operation within and between the various groups. The Fisher exact test was used to compare patients with a satisfactory or unsatisfactory outcome to the incidence of delayed, normal, or rapid emptying after operation.

Results

Gastric Emptying

Before fundoplication 17 of the 25 patients (68%) had delayed gastric emptying. Gastric emptying was more frequently delayed before operation in patients with associated gastric pathology (81%) than in patients without (45%). When grouped, patients without gastric pathology had an emptying curve within the normal range, whereas those with gastric pathology were outside the normal

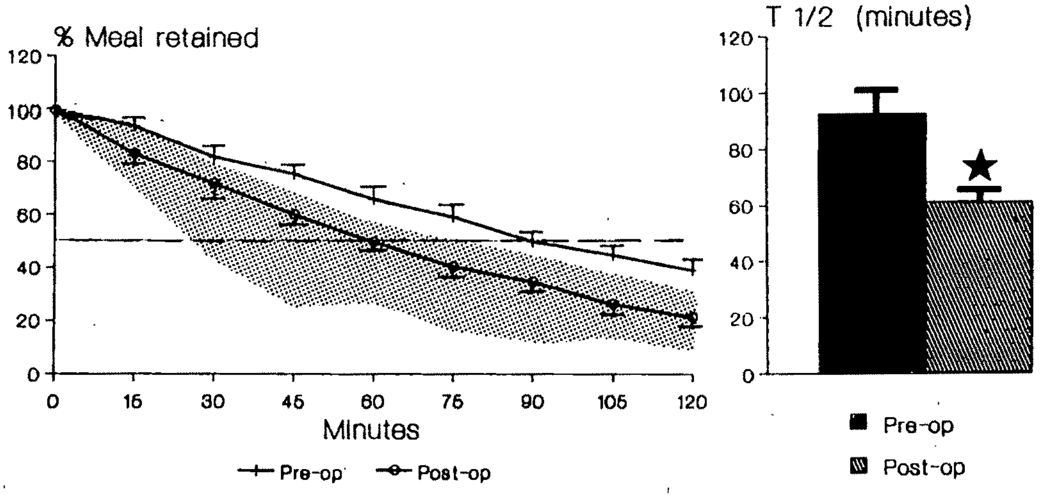


FIG. 4. Preoperative *versus* postoperative gastric emptying in the 16 patients with preoperative gastric pathology. The shaded area represents the 10th to 90th percentiles of normal. The mean T½ is illustrated in the bar graph and shows a faster rate of emptying after surgery even in the presence of gastric pathology (* = $p < 0.01$).

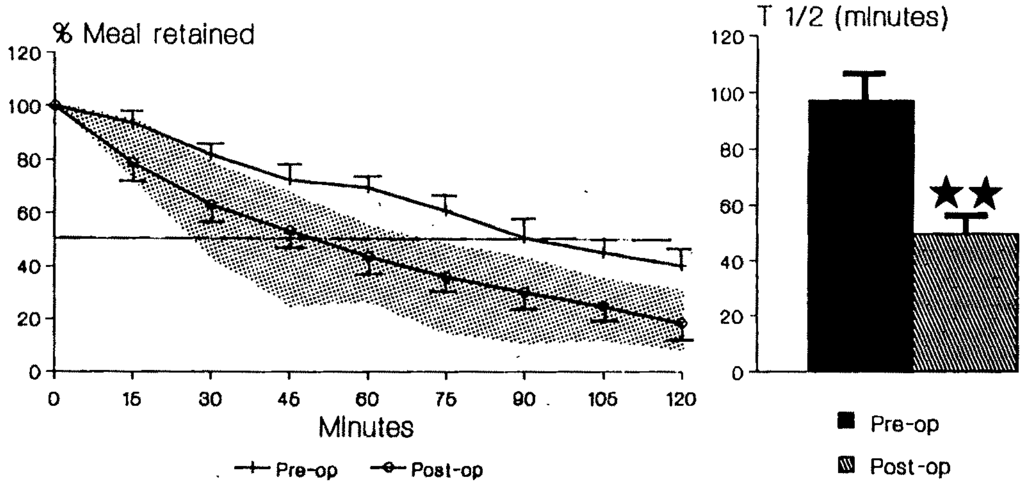


FIG. 5. Preoperative *versus* postoperative gastric emptying in nine patients with a history of ulcer disease and preoperative gastric acid hypersecretion who were treated by fundoplication and PGV. The shaded area represents the 10th to 90th percentiles of normal. The mean T½ is illustrated in the bar graph and shows the additive speeding effect of PGV and fundoplication on gastric emptying (** = $p < 0.01$).

range. The mean T½ in patients with gastric pathology was significantly higher than those without associated gastric pathology ($p < 0.05$; Fig. 1). After operation the mean gastric emptying rate of all patients was significantly faster than before operation ($p < 0.05$; Fig. 2). In patients without associated gastric pathology, fundoplication speeded gastric emptying ($p < 0.05$; Fig. 3). This normalized the emptying rate in three of the four patients who had delayed emptying before operation. Fundoplication also speeded gastric emptying in patients with associated gastric pathology ($p < 0.01$; Fig. 4). This normalized the rate of gastric emptying in 11 of 13 patients who had delayed emptying before operation. In patients in whom PGV was performed together with fundoplication, the effect of the two procedures was additive with a more marked speeding of gastric emptying than observed in patients without gastric pathology and those with untreated gastritis ($p < 0.01$; Fig. 5). This normalized the emptying rate in six of seven patients who had markedly delayed emptying before operation but resulted in abnormally rapid emptying in two patients. The five patients with gastritis who had a fundoplication alone also showed some speeding of gastric emptying ($p < 0.08$; Fig. 6).

Clinical Outcome

Follow-up evaluation showed that significant postoperative symptoms occurred in 7 of 25 patients (Table 1). Five of these seven patients had postoperative gastric emptying rates outside of the normal range, and these were either delayed or rapid (Fig. 7). Only 2 of 20 patients with normal postoperative gastric emptying had significant postoperative symptoms ($p < 0.01$). In both patients gastric pathology was present in their preoperative evaluation. All patients who had normal postoperative gastric emptying and were free of associated gastric pathology in their preoperative evaluation were asymptomatic after fundoplication.

When questioned about their satisfaction with the operation, 89% of patients without gastric pathology and

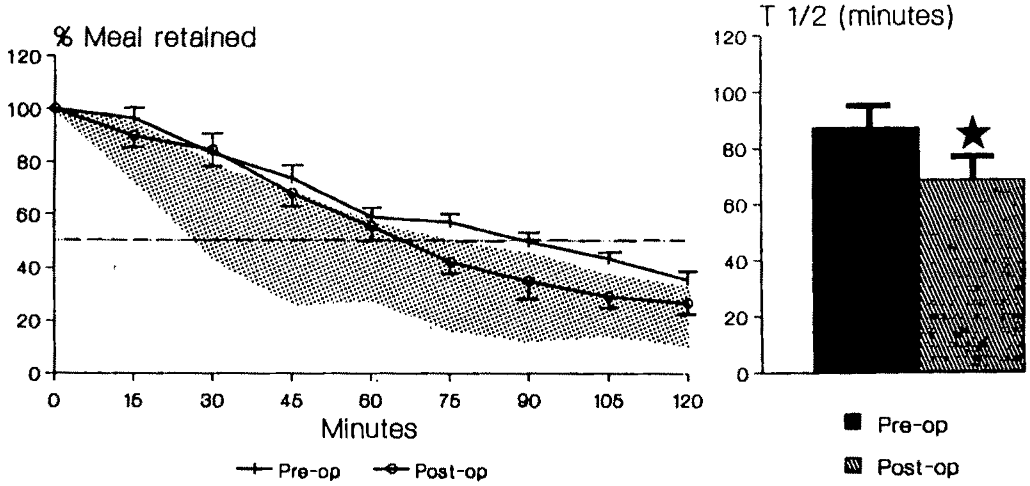


FIG. 6. Preoperative *versus* postoperative gastric emptying in five patients with gastritis alone. The shaded area represents the 10th to 90th percentiles of normal. The mean T½ is illustrated in the bar graph and shows a trend to faster emptying after fundoplication alone in patients with gastritis (*= $p < 0.08$).

TABLE 1. *Symptoms and Postoperative Gastric Emptying in the Seven Patients with an Unsatisfactory Outcome*

Symptoms	Postoperative Gastric Emptying
No Gastric Pathology (Nissen only)	
Chest pain and regurgitation	Delayed
Gastric Pathology (Nissen only)	
Epigastric pain, nausea	Normal
Epigastric pain, nausea, heartburn*	Delayed
Gastric Pathology (Nissen plus PGV or BDP)	
PGV Diarrhea	Rapid
PGV Epigastric pain, nausea	Rapid
PGV Dumping, nausea	Normal
BDP Diarrhea, constipation	Delayed

* Breakdown of fundoplication.

PGV, proximal gastric vagotomy; BDP, bile diversion procedure.

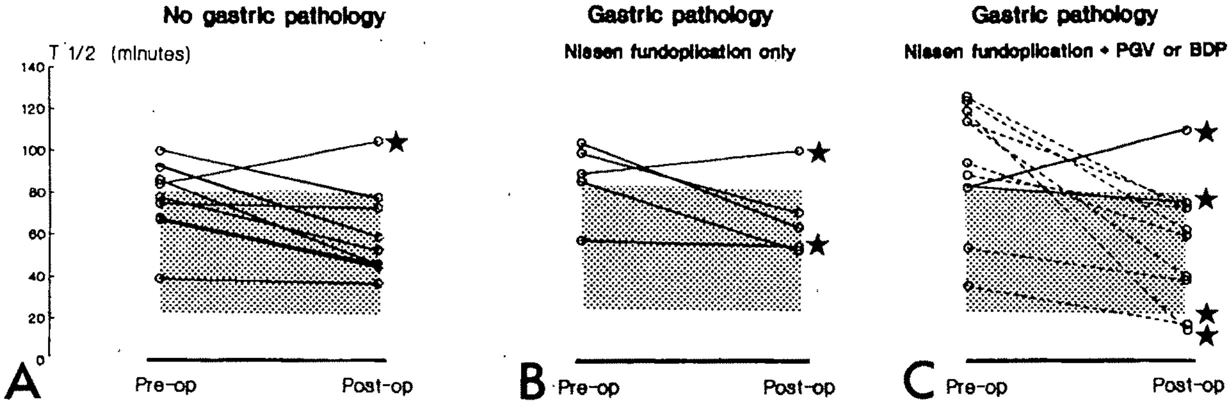
81% with associated gastric pathology were satisfied with the result of the operation (Table 2). Seventy-seven per cent of patients without and 63% with associated pathology believed that the operation has cured their disease. The remaining patients all believed that the operation had improved their condition. No patient stated that the operation worsened his condition. All the patients without and 93% with associated gastric pathology were satisfied with the result of surgery and if they had to make the decision to have the operation again they would do so again in light of their current experience.

Discussion

Increased esophageal exposure to gastric juice and abnormal gastric emptying are common findings in patients with foregut symptoms.[1] We have shown previously that both abnormalities occur independently of each other and that the incidence of delayed gastric emptying is similar in those with or without gastroesophageal reflux[1] (Fig. 8). The present study consists of patients with documented gastroesophageal reflux. One third of these patients had no concomitant gastric pathology, 45% of whom had delayed gastric emptying, and two thirds had concomitant gastric pathology, 81% of whom had delayed emptying. This raises the question why gastric emptying is delayed in a large proportion of patients with increased esophageal exposure to gastric juice even in the absence of gastric pathology. There are at least three possibilities. First the delay in gastric emptying could be due to venting of fundic pressure into the esophagus through a mechanically defective sphincter. Second delayed gastric emptying could be due to neutralization of fundic pressure by the effect of the negative thoracic pressure on the intrathoracic portion of the stomach in patients with a hiatal hernia. Third patients with a mechanically defective lower esophageal sphincter may also have a muscle abnormality involving the gastric fundus, resulting in decreased fundic tone.

Reduction of the radius of the proximal stomach by fundoplication increased the rate of gastric emptying in our study. This resulted in normalization of emptying in 13 of 17 patients with delayed preoperative gastric emptying. The mechanism by which this happened could be explained by Laplace's Law, which states that a decrease in radius results in disproportionately less wall tension required to generate a greater intraluminal pressure. This would promote the fundic contribution to the forward passage of chyme. Wilbur and Kelly[11] have shown previously that reducing the radius of the proximal stomach by fundectomy in dogs resulted in a speeding of the rate of gastric emptying of liquids.

Of the 25 patients, 17 had delayed gastric emptying before operation and none had rapid emptying. An un-



FIGS. 7A–C. Individual pre- and postoperative T½ in patients grouped according to (A) no gastric pathology, (B) untreated gastric pathology, and (C) treated gastric pathology. PGV = proximal gastric vagotomy (dotted lines) and BDP = bile diversion (solid lines C only). The shaded area represents the 5th and 95th percentiles of normal. The stars indicate the seven patients with an unsatisfactory outcome, five of whom had abnormal postoperative gastric emptying. Of the 20 patients with normal postoperative gastric emptying only two had an unsatisfactory outcome.

satisfactory outcome occurred in every patient in whom gastric emptying was not normalized after operation. Based on this finding, the side effects of fundoplication, other than dysphagia and the inability to vomit or belch, are more a consequence of the failure to normalize gastric emptying than of the procedure. Our findings show that the persistence of delayed gastric emptying after operation was most likely due to the presence of concomitant gastric pathology. Only two of the 20 patients with normal postoperative gastric emptying had an unsatisfactory outcome. In one the symptoms were most likely due to induced dumping and the other from persistent gastric mucosal damage secondary to duodenogastric reflux. These results suggest that to disregard or fail to recognize mild gastric pathology is the most common cause of an unsatisfactory outcome. This may explain the high incidence of burning epigastric pain induced by eating, postprandial fullness, and postprandial distention reported by Negre[3] after Nissen fundoplication. It is important that from the patient's point of view the benefit derived from fundoplication in controlling reflux outweighs the side effect. This point was underscored by the report that 100% of the patients without and 93% with gastric pathology would have the operation again.

In some patients damage to the vagus nerves while performing the fundoplication, particularly when associated with a PGV, may induce postoperative symptoms or make existing gastric-based symptoms worse. This was suggested by the observation that one patient without and one with gastric pathology developed further delay of their emptying after fundoplication and two patients with gastric pathology developed rapid emptying after fundoplication and PGV. The former could be explained by postvagotomy gastric stasis and the latter by the dumping syndrome. Vansant and Baker[12] reported that the incidence of specific symptoms of delayed emptying, such as bloating, nausea, and vomiting, were almost identical after an antireflux procedure, regardless of the addition of truncal vagotomy, but the incidence of diarrhea and dumping was significantly increased in vagotomized patients. This suggests that vagotomy is unlikely to cause delayed gastric emptying in patients with reflux disease and supports our observation that proximal gastric vagotomy and fundoplication can actually speed gastric emptying. Performing a PGV can cause dumping and diarrhea and, because it does not contribute to the control of reflux, should be reserved for those patients with a history of ulcer disease and documented hypersecretion.

TABLE 2. *Patient Satisfaction After Operation*

Degree of Satisfaction	No Gastric Pathology (%)	Gastric Pathology (%)
Cured	77	63
Improved	23	37
Worsened	0	0
Satisfied	89	81
Would have operation again	100	93

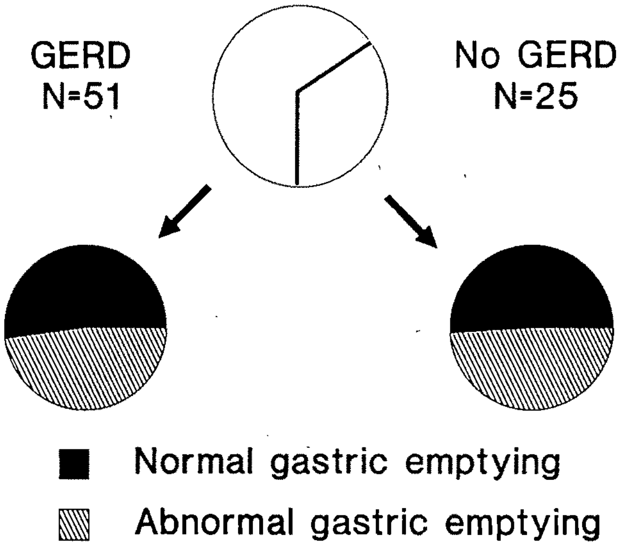


FIG. 8. Similar incidence of abnormal gastric emptying in patients with foregut symptoms with or without gastroesophageal reflux.

It was not possible to predict the pattern of postoperative gastric emptying from the pattern of preoperative emptying. Five of the patients with an unsatisfactory outcome had delayed preoperative emptying and the remaining two had normal emptying. This was similar to the ratio found in patients with a satisfactory outcome. This emphasizes that postoperative side effects of fundoplication, other than dysphagia and the inability to vomit or belch, can come from persistent delayed gastric emptying, persistent gastric mucosa damage, or rapid emptying from an inadvertent truncal vagotomy.

We used radiolabeled oatmeal as the test meal because it is convenient to use, well tolerated by the patients, and adequately reflects the characteristics of a liquid and a solid meal.[1] We used two methods to assess the rate of gastric emptying, both based on the rate of emptying in a normal population: If the $T\frac{1}{2}$ fell outside the 95th and 5th percentile of normal or if the emptying curve remained outside of the 90th and 10th percentile of normal after 90 minutes it was regarded as abnormal. There was total agreement between the two methods in the preoperative evaluation of gastric emptying. After operation some patients showed rapid initial gastric emptying that was more accurately identified by the $T\frac{1}{2}$ method. Similarly regression lines or expression of the rate of emptying as percentage emptied per minute would have been less accurate when emptying was no longer linear in nature.

This study has shown that most patients with gastroesophageal reflux disease without concomitant gastric pathology have normal gastric emptying after fundoplication and that these patients have minimal side effects from the operation. Those who remain outside the normal range are very likely to have postoperative symptoms. The presence of concomitant gastric pathology should not be ignored because it may be associated with delayed gastric emptying and persistent postoperative symptoms. On the other hand, surgical treatment of the concomitant gastric pathology should not be undertaken lightly because the additional procedure might alter gastric emptying and contribute to an unsatisfactory outcome.

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DISCUSSION

DR. C. THOMAS BOMBECK III (Chicago, Illinois): The authors have very bravely attacked what was initially a very simple problem and what is now a very complicated one. In the late 1970s, there were several reports that patients with gastroesophageal reflux had delayed gastric emptying. Indeed I believe that when Dr. DeMeester was at the University of Chicago he reported one of the first of these. In 1985 it was first reported that the Nissen fundoplication corrected the delayed gastric emptying, normalizing it or at least accelerating it from the preoperative levels.

More recently, in our own laboratories, Drs. Carrallho and Richter have demonstrated in the experimental animal that a Wendell cardioplasty, a mechanical procedure that destroys the lower esophageal sphincter without at all endangering the vagi or impinging on the stomach, markedly increases or delays gastric emptying. We have questioned exactly why this occurs. Now we are trying to sort out whether it is due to acid contact with the esophageal mucosa producing, if you will excuse the pun, a reflux-reflex inhibition of gastric emptying, or if it is due to a simple mechanical effect, venting of gastric fundic pressure thereby destroying the efficiency of gastric peristalsis.

I would first like to ask the authors why they think some patients do have delayed gastric emptying. Second the authors demonstrated a group of patients who had no evidence of gastric pathology, some of whom had delayed gastric emptying and others who did not. There must be a difference between those two groups of patients. It is interesting to speculate that it might be in the degree of LES failure.

Two years ago before this association we presented a method of quantitating LES sphincter strength, which was considerably more detailed than the standard pull-back procedure, and I wonder if the authors have used that or any other in an attempt to distinguish these two groups of patients. Do patients with delayed emptying have a worse degree of LES failure than patients without?

At the same time that all of this has been going on, we have known very well that various types of gastric pathology have caused delayed gastric emptying, such as gastric outlet obstruction for one reason or another or gastric mucosal disease. This causes us to wonder, in terms of reflux and delayed emptying, which was coming first, the chicken or the egg? The results that you have heard here today seem to suggest that they arrive simultaneously. In fact it seems that these authors have defined two groups of patients. Those who have delayed gastric emptying because they have gastric pathology and those who have delayed gastric emptying because they have a failed lower esophageal sphincter. It would seem to be of great importance to be able to define those two groups of people before operation.

Would the authors recommend, therefore, that all patients should have studies of gastric emptying, perhaps gastric secretory studies, before they have a Nissen fundoplication? If not, why not?

DR. JAMES A. O'NEILL, JR. (Philadelphia, Pennsylvania): Dr. Hinder and his colleagues clearly describe that some patients with gastroesophageal reflux have delayed gastric emptying, and that the incidence of this problem in his patients may be as high as two thirds of those with gastroesophageal reflux. This is important because, at least in the past, some have suggested that some sort of gastric emptying procedure should be performed in such cases.

This very suggestion led us to look at this issue 5 years ago when we reported 18 patients with reflux strictures of the esophagus to this Association. At that time, we noted that 4 of our 18 patients had delayed emptying, and all of these patients were carefully studied. In all of these patients, the emptying normalized after operation following a Nissen fundoplication.

Recently one of our fellows reviewed more than 200 patients in whom a Nissen fundoplication was done. The incidence of delayed gastric emptying was 25%. It was 20%, as you saw in the reflux stricture group. Now what was noted, however, was that the majority of these patients had severe esophagitis. This leads me then to ask three questions. Why do you think that your incidence is 2.5 to 3 times what we have seen in our patients, although I must say the fact that our patients were children would place them in your no gastric pathology group? We have followed our patients with both milk technetium scans and scrambled egg scans as opposed to oatmeal.

Do you think that esophagitis is an issue in etiology that would perhaps suggest that the lower esophageal sphincter is to be indicted? And finally, as you did, I think all of us have rare patients who are not relieved after operation, and I wonder, does your data help you to identify these patients so that perhaps gastric emptying procedures could be applied selectively and appropriately?

DR. CARLOS PELLEGRINI (San Francisco, California): Indeed this paper illustrates some interesting physiologic and pathologic aspects that have direct clinical application.

In your paper you tell us that 64% of the patients had associated gastric pathology. Would you please define what you consider gastric pathology? Second why is there such a high incidence of gastric pathology in association with abnormal gastroesophageal reflux? Were these patients selected, or does this represent a consecutive series of patients?

You found that nine patients with gastric hypersecretion also had delayed gastric emptying. By contrast most other authors have found that patients with gastric hypersecretion have rapid gastric emptying. The typical case is that of patients with Zollinger-Ellison syndrome who empty very rapidly. Could you tell us what is your interpretation of this rapid emptying?

The finding of rapid gastric emptying after Nissen fundoplication is, in my opinion, not surprising. Dr. Kelly showed rapid gastric emptying in dogs after fundectomy of the stomach, and I believe that the wrap in the Nissen fundoplication uses most of the gastric fundus. This deprives the stomach of its reservoir capacity and therefore rapid gastric emptying is to be expected. On the other hand we have shown that, in most cases, rapid gastric emptying is well tolerated and that few patients with rapid gastric emptying after gastric surgery complain of symptoms.

My final question has to do with the message of this study. Because of this common association with gastric pathology, are you suggesting that all patients with abnormal gastroesophageal reflux ought to be evaluated in terms of gastric secretion and motility? And if your answer is yes, how should we apply the results of these tests in planning the operation? For example, would you advise the addition of a parietal cell vagotomy in an asymptomatic patient with gastric hypersecretion who is operated on for abnormal reflux?

DR. ERIC W. FONKALSRUD (Los Angeles, California): I would also like to congratulate Drs. Hinder and DeMeester and their colleagues on an excellent presentation and for providing us with helpful and new information regarding the relationship of gastroesophageal reflux and delayed gastric emptying. Although there may be some differences in what you have observed in adults and what we see in young children, particularly those with central nervous system disorders, there may be more similarities than previously realized. More than 50% of both adults, as indicated in today's presentation, and young children with symptomatic reflux have delayed gastric emptying before operation. Although reduction of gastric volume by fundoplication may enhance gastric emptying transiently, approximately one fourth of the patients in the present study had symptomatic gastric dysmotility after operation, which is similar to our experience with children.

How long does the accelerated emptying after the fundoplication persist? Is this a matter of months or years? Have you performed a subsequent pyloroplasty on any of the five patients who had postoperative symptomatic delay in gastric emptying?

Fourteen children in our hospital required reoperation with pyloroplasty when gastric emptying subsequently showed more than 70% isotope retention at 90 minutes. None of these patients had apparent vagal injury from the fundoplication. A competent fundoplication combined with postoperative delay in gastric emptying may produce a form of closed loop obstruction, particularly in children who are often quite aerophagic. We now routinely study gastric emptying in all children with symptomatic reflux and have found a severe delay in more than 15% of patients. We have, therefore, combined a loose fundoplication with a pyloroplasty in most of these children. Repeat gastric emptying studies 6 weeks to 1 year after operation have shown less than 50% isotope retention at 90 minutes in each of the 68 children who underwent pyloroplasty combined with fundoplication.

The incidence of gas bloat and slipped or malfunctioning fundoplication has been reduced to less than 5% because pyloroplasty has been used more frequently in our experience. Before this time we had a much higher incidence of slipped Nissen fundoplications and other complications.

Have you been able to identify before operation which of your refluxing patients will have symptomatic delay in gastric emptying after fundoplication?

DR. JONATHAN E. RHOADS (Philadelphia, Pennsylvania): We have been impressed with the relationship between the time of gastric emptying and the level of serum proteins. I thought particularly in relationship to the first chart comparing the patients with gastric pathology and those without that I would like to know what the serum proteins were in the two groups and whether this has been controlled?

DR. RONALD HINDER (Closing discussion): I would like to thank all the discussants for their interesting questions. First Dr. Bombeck. I was interested to hear that you found delayed gastric emptying to occur after the Wendell gastroplasty. This lends support to the concept of venting of intragastric pressure into the esophagus through an incompetent sphincter; however this is not supported by our previous studies (Schwizer W, et al. Am J Surg 1989; 157:74–81) in which we showed that there was no relationship between sphincter competence and delayed gastric emptying in patients with foregut symptoms. The hiatal hernia lying in the negative intrathoracic pressure probably plays a role in delaying gastric emptying. It is also possible that lower esophageal pathology may also involve the proximal stomach, on the one hand producing reflux and on the other hand producing delayed gastric emptying. You also asked about sphincter vector volume. We are aware of the work that you have done and are also now measuring sphincter volume, but not on the patients in this study who all had conventional sphincter manometry. Concerning preoperative evaluation of the patients we found that there was no way that we could predict by our preoperative evaluation what the postoperative outcome would be.

As far as Dr. O'Neill is concerned, he conceded that in children the disease may be different than that seen in adults. There must, however, be some similarities, as Dr. Fonkalsrud suggested. The difference in adults is that we see more associated gastric pathology than in children, and this probably caused the delayed gastric emptying that we saw in our patients as opposed to that reported in children.

Dr. Pelligrini asked about our high incidence of patients with gastric pathology. These were not consecutive patients. They were problem patients and so obviously had a high incidence of gastric pathology. He asked whether we should do all of these tests routinely in our patients. In most patients we don't need to have all of this information and reserve this detailed testing for patients for whom our clinical judgment would suggest that it is required.

Dr. Fonkalsrud wished to know how long after operation we had carried out our gastric emptying tests and whether the results would change with time. We carried out our tests from between 1 and 35 months after surgery with a median of 12 months. We found that the results were similar in those tested early after surgery compared to those long after surgery. He raised the question whether pyloroplasty should be used in patients with delayed gastric emptying. This procedure should not be used routinely in patients with delayed gastric emptying because pathologic duodenogastric reflux may be the cause of the problem in some patients and could be enhanced by pyloroplasty.

Finally Dr. Rhoads asked if we knew the serum protein values in our patients. The patients were generally well nourished and I would assume that the serum proteins were normal.

Relationship Between Admission Hyperglycemia and Neurologic Outcome of Severely Brain-Injured Patients

BYRON YOUNG, M.D., LINDA OTT, M.S., ROBERT DEMPSEY, M.D., DENNIS HAACK, PH.D., and PHILLIP TIBBS, M.D.

Severe head injury is associated with a stress response that includes hyperglycemia, which has been shown to worsen outcome before or during cerebral ischemia. To better define the relationship between human head injury and hyperglycemia, glucose levels were followed in 59 consecutive brain-injured patients from hospital admission up to 18 days after injury. The patients who had the highest peak admission 24-hour serum glucose levels had the worse 18-day neurologic outcome ($p = 0.01$). Patients with peak 24-hour admission glucose levels greater than 200 mg/dL had a two-unit increase in Glasgow Coma Scale score while patients with admission peak 24-hour serum glucose levels less than or equal to 200 mg/dL had a four-unit increase in Glasgow Coma Scale score during the 18-day study period ($p = 0.04$). There was a significant relationship between 3-month and 1-year outcome and peak admission 24-hour serum glucose level ($p = 0.02$ and $p = 0.02$, respectively). Those patients with admission peak 24-hour serum glucose levels less than or equal to 200 mg/dL had a greater percentage of favorable outcome at 18 days, 3 months, and 1 year than those with admission peak 24-hour glucose levels greater than 200 mg/dL ($p = 0.0007$, $p = 0.03$, and $p = 0.005$, respectively). A significant relationship between admission peak 24-hour Glasgow Coma Scale score and 18-day, 3-month, and 1-year outcomes was found ($p = 0.0001$, $p = 0.0002$, and $p = 0.0002$, respectively). Patients with mean admission peak 24-hour Glasgow Coma Scale scores of 3.5, 6, and 10 had mean admission 24-hour peak serum glucose levels of 252 ± 23.5, 219.1 ± 19, and 185.8 ± 21, respectively ($p = 0.05$). These relationships were not significantly altered when confounding variables such as the amount of glucose given over the initial 24-hour postinjury period, the presence of diabetes or multiple injuries, and whether patients were given steroids, dilantin, or insulin were statistically incorporated. These data suggest that admission hyperglycemia is a frequent component of the stress response to head injury, a significant indicator of severity of injury, and a significant predictor of outcome from head injury.

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SEVERE HEAD INJURY is associated with an acute sympathoadenomedullary response characterized by increased blood levels of norepinephrine, epinephrine, and dopamine.[1-3] The levels of circulating catecholamines are inversely related to the severity of brain injury.[1] Rosner et al.[3] showed that hyperglycemia occurred within minutes of experimental head injury in cats. In this animal model, hyperglycemia was related to severity of injury and was thought to be caused by catecholamine release. The relationship between human head injury and blood glucose levels has not been determined. We report a significant relationship between hyperglycemia and severity of human brain injury.

Methods

Fifty-nine consecutive brain-injured patients were studied from hospital admission to 18 days after injury. All had peak 24-hour Glasgow Coma Scale (GCS) scores between 4 and 10 during the first 24 hours of hospital admission. The ratio of male patients to female patients was five to one, and the mean age of the patients was 31.4 years. The mean admission peak 24-hour GCS score was 6.9. The primary injury in all patients was to the brain, and 28% of patients had extracranial injuries including rib or long-bone fractures, pneumothoraces, or abdominal injuries. Forty-eight per cent of patients had closed head injuries, 21% had gunshot wounds, 9% had depressed skull fractures with brain contusions, and 22% suffered hematomas.

The amount of glucose infused during the first 24 hours after injury was ascertained. Serum glucose levels were obtained on admission to the emergency unit, three times per day while in the intensive care unit, and daily while

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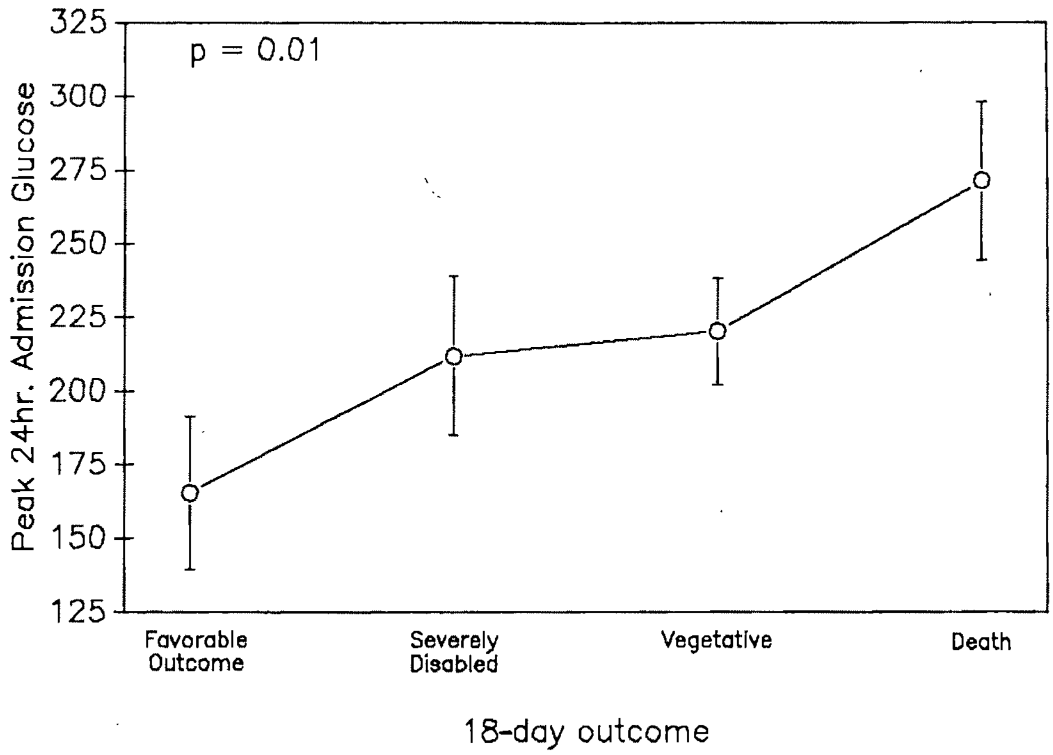

FIG. 1. Peak 24-hour admission serum glucose level *versus* Glasgow Outcome Scale score 18 days after injury in 59 severely head-injured patients. All values are mean ± SEM.

in the hospital ward. Control of serum glucose levels greater than 200 mg/dL was attempted by treatment with insulin and withholding of intravenous dextrose solutions. No patients received corticosteroids after admission to our unit. Twenty per cent of patients were given corticosteroids once for cerebral edema by the referring physician. Preinjury presence of diabetes was noted, as was the use of Dilantin (Parke-Davis, Division of Warner-Lambert, Co., Morris Plains, NJ).

Daily peak serum glucose levels were obtained for the first seven days after injury. Daily peak GCS score was determined for the first 18 days after injury. Neurologic outcome was assessed by the Glasgow Outcome Scale (GOS) at 18 days, 3 months, 6 months, and 1 year after injury. Neurologic outcome at 18 days, 3 months, and 1 year, and admission GCS were evaluated in relationship to peak daily serum glucose levels.

Statistics

Comparison of serum glucose levels by outcome was made by one-way analysis of variance (ANOVA). Significance reflects a test for linear effect when outcome classes are equally spaced or when using the midpoint of classes, and adjustment for 24-hour glucose infusion was by covariate analysis of variance. The outcome classes are death, vegetative, severely disabled, and good recovery (moderately disabled and favorable outcome). Change in GCS from days 1 to 18 for patients with high and low admission glucose was assessed by repeated measures of ANOVA, while adjustment for 24-hour glucose infusion was by covariate analysis of variance. Percentages of favorable outcome by high or low admission glucose were evaluated by the chi square test. The relationship between GCS, glucose level, and outcome was assessed by a correlation coefficient, while a partial correlation coefficient was used to evaluate the independence of these relationships, as well as to adjust for 24-hour glucose influence. The means reported in Table 1 are least square means that reflect the adjustment for 24-hour glucose infusion.

Results

Forty-eight per cent of the patients had peak admission glucose levels greater than 200 mg/dL, 26% had levels between 160 and 200 mg/dL, and 26% were less than 160 mg/dL. Only four patients had peak 24-hour admission serum glucose levels less than 120 mg/dL. The patients who had the highest peak admission 24-hour serum glucose levels had the worst 18-day neurologic outcomes ($p = 0.01$). Patients with 18-day outcomes of death, vegetative, severe disability, and moderate or good recovery had mean 24-hour admission peak blood glucose levels of 271.6 ± 27, 220.4 ± 18, 212.1 ± 27, and 165.5 ± 26, respectively (Fig. 1). Patients with peak 24-hour serum glucose levels greater than 200 mg/dL had a two-unit increase in GCS score during the 18-day study period, while patients with admission peak 24-hour serum glucose levels

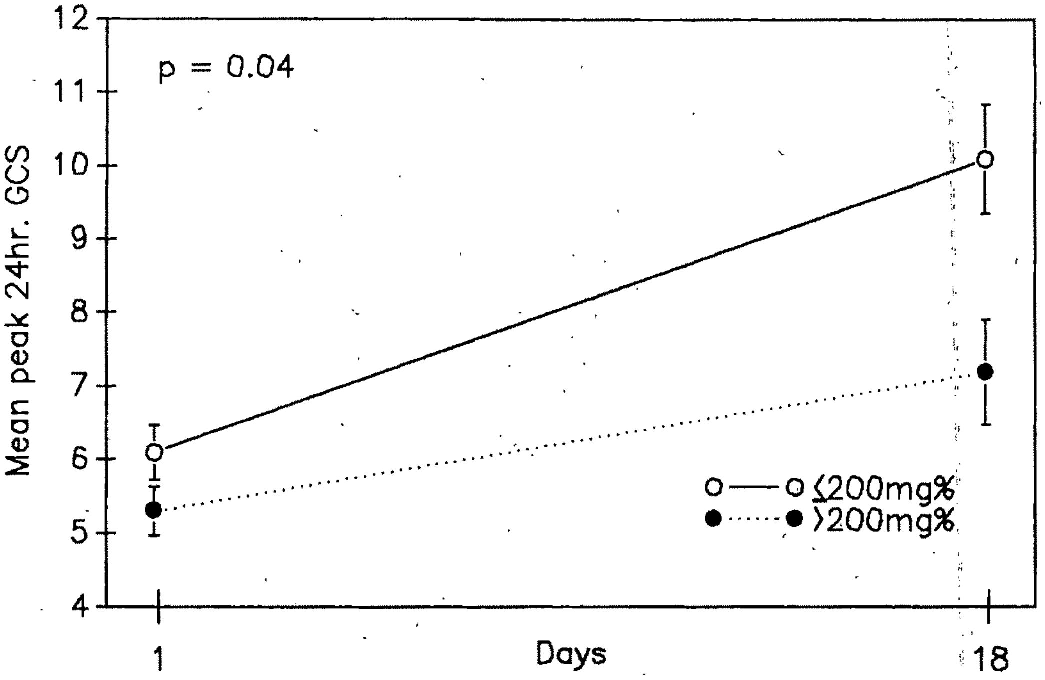

FIG. 2. Glasgow Coma Scale score one day and 18 days after injury in patients with serum admission peak 24-hour glucose levels less than or equal to or greater than 200 mg%. All values are mean ± SEM.

less than 200 mg/dL had a four-unit increase in GCS score during the 18-day study period (p = 0.04; Fig. 2). There was a significant linear trend for 3-month and 1-year outcomes and admission peak 24-hour serum glucose level (p = 0.02, p = 0.02, respectively; Figs. 3 and 4). Patients with admission peak serum glucose levels less than or equal to 200 mg/dL had a greater percentage of favorable outcomes at 18 days, 3 months, and 1 year than those with admission peak 24-hour glucose levels greater than 200 mg/dL (p = 0.0007, p = 0.03, and p = 0.005, respectively; Fig. 5). There was a significant relationship between admission peak 24-hour GCS score and 18-day,

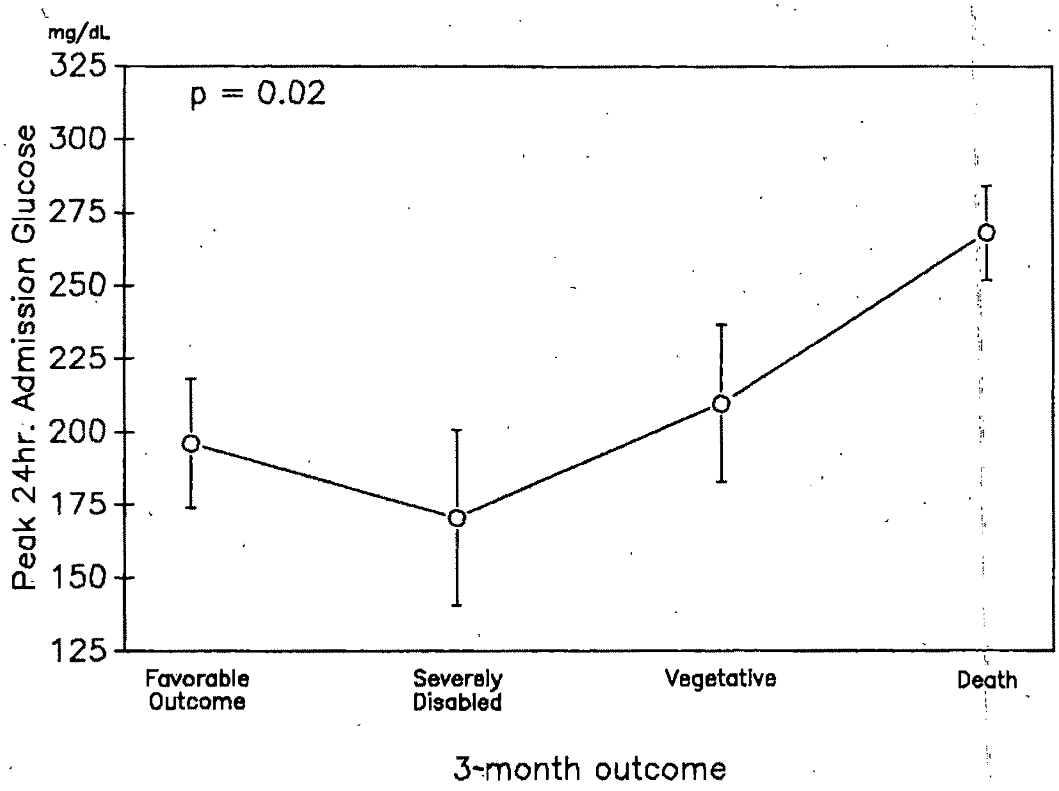

FIG. 3. Peak 24-hour admission serum glucose level *versus* Glasgow Outcome Scale score 3 months after injury in 59 severely head-injured patients. All values are mean ± SEM.

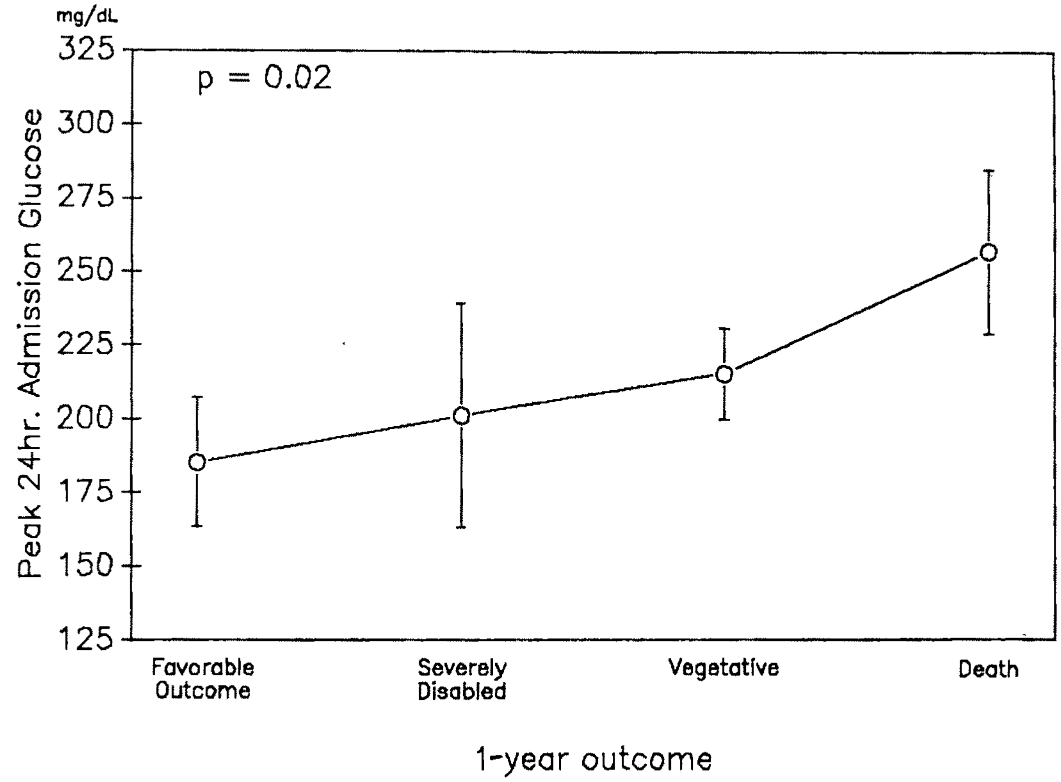

FIG. 4. Peak 24-hour admission serum glucose level *versus* serum Glasgow Outcome Scale score 1 year after injury in 59 severely head-injured patients. All values are mean ± SEM.

3-month, and 1-year outcomes (p = 0.0001, p = 0.0002, p = 0.0002, respectively). Although admission glucose levels were also significantly related to 18-day, 3-month, and 1-year outcomes, this relationship tended to disappear when adjustment was made for admission peak 24-hour GCS. Admission peak 24-hour glucose levels were significantly related to admission peak 24-hour GCS score (p = 0.05). Patients with admission mean peak 24-hour GCS scores of 3.5, 6, and 10 had mean admission 24-hour peak serum glucose levels of 252 ± 23.5, 219.1 ± 19, and 185.8 ± 21, respectively (Fig. 6). Statistical inclusion of the amount of glucose administered to patients within the first 24 hours did not significantly affect the results (Tables 1 to 3). The percentages were not remarkably altered for

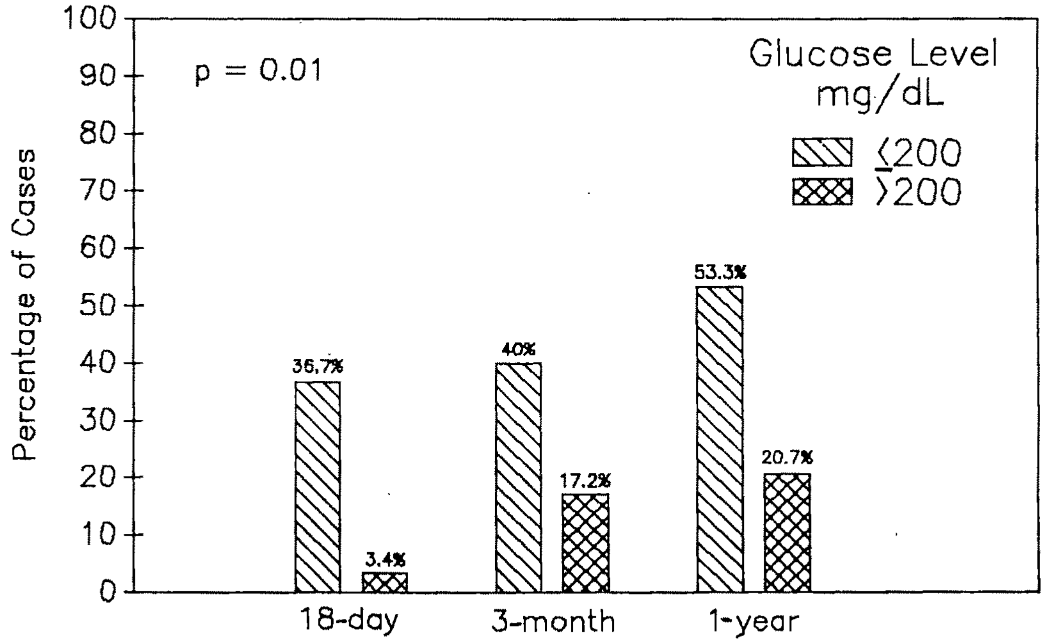

FIG. 5. Percentage of patients with favorable outcomes 18 days, 3 months, and 1 year after injury in patients with peak 24-hour admission serum glucose levels less than or greater than 200 mg%. All values are percentages.

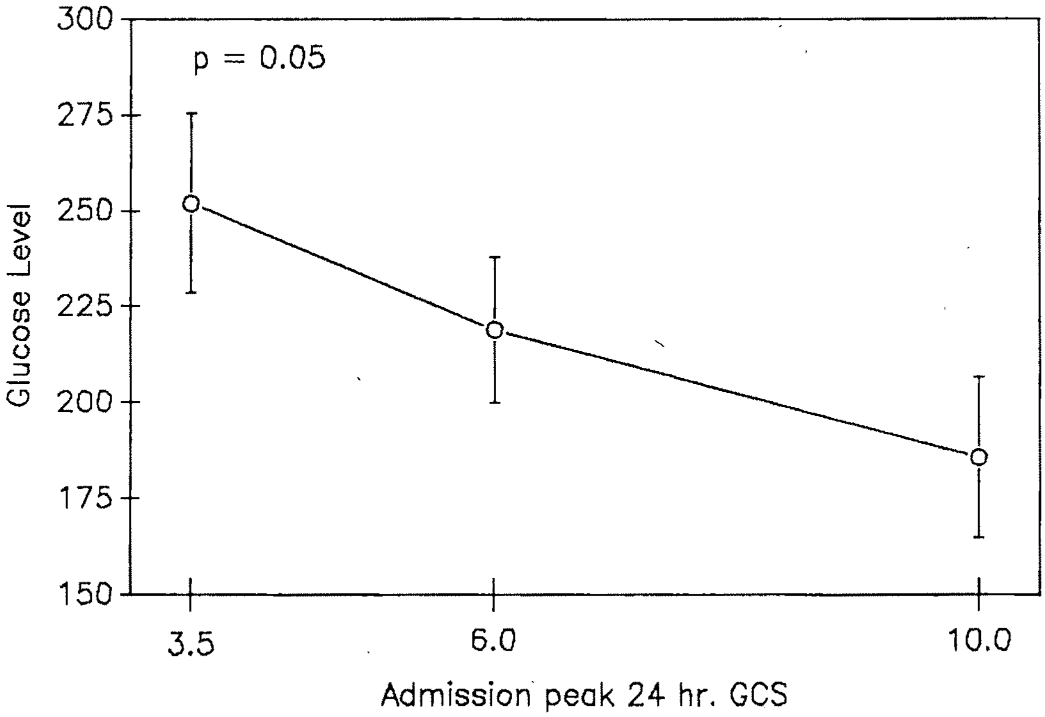

FIG. 6. Peak admission 24-hour serum glucose level *versus* peak admission 24-hour Glasgow Coma Scale score in 59 severely head-injured patients. All values are mean ± SEM.

patients given or not given Decadron (Merck Sharp and Dohme, West Point, PA), with or without systemic injuries, given or not given insulin, with or without diabetes, and given or not given dilantin, with the exception of patients on Decadron (1-year outcome) (Table 4). No relationship between serum glucose levels and outcome could be found after the first day after injury.

Discussion

This study showed that admission peak 24-hour GCS scores and admission peak 24-hour serum glucose levels are significantly related, despite the presence of confounding variables such as glucose, steroid, dilantin, or insulin administration and the presence of multisystem injury or diabetes. Hyperglycemia is a component of the stress response to injury.[4] Blood glucose levels have been shown by Rosner[3] to be elevated in the cat experimental head injury model. Rosner et al.[3] speculated that hyperglycemia and increased blood catecholamines were causally related. Catecholamines and glucagon stimulate the breakdown of glycogen stored in the liver into glucose.[4,5] Bessey et al.[6] have shown in normal humans that a triple hormone infusion (glucagon, catecholamines, and cortisol) causes hyperglycemia similar to that observed in mild to moderate stress. A single hormone infusion of either catecholamines, glucagon, or cortisol alone did not cause hyperglycemia. This finding suggests a synergistic hormonal effect after injury.

TABLE 1. *Mean (±SEM) Admission 24-Hour GCS* Versus *Admission Peak 24-Hour Glucose Level*

	Linear Effect	
Admission Peak 24-Hour GCS	Mean (±SEM) Admission Peak 24-Hour Glucose Level (mg/dL)	Column II Parameters Adjusted for 24-Hour Glucose Infusion (mg/dL)
3–4 (3.5)	252.0 (±23.94)	236.5 (±21.76)
5–7 (6)	219.1 (±19.15)	203.8 (±21.17)
>8	184.1 (±22.57)	191.6 (±25.06)

p value = 0.05; p = 0.21.

Catecholamines increase glucagon secretion and inhibit insulin secretion after injury and stress.[5] The mechanism of sympathetic system activation has not been resolved. Specific focal hypothalamic and/or brain stem injury and diffuse white matter injury may be responsible.[7] Alternately the release of interleukin-1, the cytokine mediating the acute phase response, could play a role.[8]

There is a considerable body of evidence from human and animal studies to show that hyperglycemia increases

TABLE 2. *Outcome Class* Versus *GCS Class*

	p Values		
	18-Day	3-Month	1-Year
Unadjusted	0.01	0.02	0.02
Adjusted for 24-hour glucose infusion	0.03	0.08	0.05

TABLE 3. *Partial Correlations and Value for GOS* Versus *GCS*

Neurologic Outcome	Partial Correlation and p Value for GOS *Versus* GCS	Column II Parameters Adjusted for 24-hour Glucose Infusion
18-day	−0.24 (0.07)	−0.22 (0.12)
3-month	−0.20 (0.13)	−0.17 (0.23)
1-year	−0.21 (0.11)	−0.17 (0.22)

the morbidity and mortality produced by cerebral ischemic insults such as cardiac arrest and stroke.[9,10] During normal aerobic metabolism, glucose is converted into pyruvate.[11] Pyruvate then enters the Kreb's cycle as a source of energy (ATP). When the supply of oxygen is limited, pyruvate is alternatively reduced to lactate. Increased levels of lactate and low pH damages brain cells.[12] The mechanisms for increased ischemic damage to brain in the presence of hyperglycemia are (1) anaerobic metabolism in which glucose is converted to lactate rather than pyruvate, and (2) increased levels of glucose, available for lactate production, that lead to secondary neuronal damage due to lactate accumulation.

Other investigators have observed relationships between degree of hyperglycemia and neurological outcome. D'Alecy et al.[13] demonstrated that dogs randomly infused with 5% dextrose in lactated Ringer's solution that underwent subsequent cardiac arrest had significantly increased neurologic deficits 24 hours after injury compared to a control group infused with lactated Ringer's solution. Serum hyperglycemia was evident in the group with the worst neurologic outcome. Longstreth et al.[14] showed a relationship between blood glucose and neurologic recovery after cardiac arrest in 430 patients. Mean blood glucose at the time of hospital admission was higher in the 154 patients who never awakened than in 276 patients who did awaken ($p < 0.05$). Among the latter group, 90 patients with persistent neurologic deficits had higher serum glucose levels than those without persistent deficits ($p < 0.02$). Pulsinelli et al.[15] found that patients with ischemic stroke who had blood glucose levels greater than 120 mg/dL at hospital admission had a significantly worse neurologic outcome than those with blood glucose levels less than 120 mg/dL. Less than one half (43%) of those with blood glucose levels exceeding 120 mg/dL were able to return to gainful employment, whereas three fourths (76%) of those with low blood sugar were able to do so. Pulsinelli et al.[16] found that increasing blood glucose levels, two- or threefold, in rats subjected to four-vessel occlusion significantly worsened ischemic brain damage. Pentelenyi et al.[17] correlated blood glucose and serum insulin levels with level of consciousness in head-injured patients. Merguerian et al.[18] described an association between hyperglycemia (glucose > 270 mg%) and a high mortality rate in head-injured patients.

TABLE 4. *Admission Peak 24-Hour Glucose* Versus *Outcome (Favorable, Unfavorable)**

Group	% Favorable (18 days)	
	Glucose Level >200 mg%	Glucose Level ≤200 mg%
Overall	1 (3.4%)	11 (36.7%)
Decadron		
Yes (n = 18)	8.0	50.0
No (n = 41)	0.0	36.0
Systemic injury		
Yes (n = 7)	0.0	20.0
No (n = 52)	3.8	42.3
Insulin		
Yes (n = 4)	0.0	33.3
No (n = 55)	3.7	39.3
Diabetes		
Yes (n = 2)	0.0	0.0
No (n = 57)	3.7	40.0
Dilantin		
Yes (n = 20)	0.0	54.6
No (n = 39)	5.3	30.0

Group	% Favorable (3 Months)	
	Glucose > 200 mg%	Glucose ≤ 200 mg%
Overall	5 (17.2%)	12 (40.0%)
Decadron		
Yes (n = 18)	16.7	66.7
No (n = 41)	18.8	36.0
Systemic injury		
Yes (n = 7)	0.0	20.0
No (n = 52)	19.2	46.2
Insulin		
Yes (n = 4)	0.0	33.3
No (n = 55)	18.5	42.9
Diabetes		
Yes (n = 2)	0.0	0.0
No (n = 57)	18.5	43.3
Dilantin		
Yes (n = 20)	11.1	54.6
No (n = 39)	21.0	35.0

Group	% Favorable (1 year)	
	Glucose > 200 mg%	Glucose ≤ 200 mg%
Overall	6 (20.7%)	16 (53.3%)
Decadron		
Yes (n = 18)	16.7	100.0
No (n = 41)	25.0	44.0
Systemic injury		
Yes (n = 7)	0.0	40.0
No (n = 52)	23.1	57.7
Insulin		
Yes (n = 4)	0.0	33.3
No (n = 55)	22.2	57.1
Diabetes		
Yes (n = 2)	0.0	0.0
No (n = 57)	22.2	56.7
Dilantin		
Yes (n = 20)	11.1	54.6
No (n = 39)	26.3	55.0

* Favorable outcome equals good recovery and moderate disability. Unfavorable outcome equals severe disability, vegetative state, and death.

Increased brain lactate levels have been associated with hyperglycemia-induced damage. Welsh found that ischemia of 15 to 30 minutes duration caused a greater accumulation of lactic acid in the brains of glucose-infused animals than in those not infused with glucose, as well as a reduction in cortex and white matter specific gravity.[19] Ljunggren showed that serum hypoglycemia in rats was associated with a brain lactate level of 4.8 Mmoles/g, while hyperglycemia was consistent with a brain lactate level of 20.7 Mmoles/g and a significantly lower intracellular pH.[20]

Increased cerebrospinal fluid lactate levels have been observed in severely brain-injured patients. DeSalles et al.[21] found that ventricular fluid lactate concentration increased within 18 hours after injury in 19 severely head-injured patients (mean GCS on admission, 5.73). Patients with favorable outcome had a significant decrease in ventricular CSF lactate levels by 48 hours after injury. A decrease in lactate was not observed in patients with poor outcomes. Rabow et al.[22] further postulated that CSF lactic acidosis is indicative of a severe, although not necessarily intractable, disturbance of brain function associated with intracellular lactate production and acidosis.

Our data suggest that admission hyperglycemia is a frequent component of the stress response to head injury, a significant indicator of severity of injury, and a significant predictor of outcome from head injury. Studies with cerebral ischemia models show that hyperglycemia adversely affects neurologic recovery. Furthermore Rosner and Becker[23] showed in a cat head injury model that Tris infusion, which countered lactic acidosis, improved survival and morbidity. A randomized prospective study is needed to clarify whether preventing hyperglycemia after head injury improves outcome.

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DISCUSSION

DR. WILLIAM F. COLLINS, JR. (New Haven, Connecticut): I would like to discuss a different aspect before I ask a question. That aspect is how I think some of these findings fit into the studies in general of central nervous system injury. The status of patients with CNS injury when admitted to a hospital has been shown to relate to the outcome. There is the problem of determining what is the best method to treat these patients. The Glasgow coma scale has been an excellent addition to our armamentarium to place patients into mild, moderate, and severe head injury categories and has been helpful in evaluating different types of treatment, particularly when comparing different centers.

Certainly it is no surprise, as Dr. Young has pointed out, that these patients have a stress response. I think the important aspect is that the glucose measurement correlated so well with outcome.

I am sure many of you are aware that during the past 15 years diagnostic imaging has improved the ability to identify mass lesions; intracranial pressure measurements insure that cerebral perfusion is well maintained and arterial oxygen lines eliminate hypo-oxygenation. While these measures have improved CNS injury care, the improvement in the outcome of patients with head injury has plateaued, and it has plateaued at a point which, at least in the moderate-to-severe head injuries, is not acceptable to many of us.

Those of us who have been working with CNS injury, particularly spinal cord injury, have formed the hypothesis that the reaction of the central nervous system to injury causes part of the loss of function. One of the problems with the Glasgow coma scale is that it is too crude a division, particularly in moderate head injury, and perhaps glucose levels could be used. This could be important because studying methods of controlling this response to injury will certainly require multicenter trials to see whether they work. We are studying treatment of spinal cord injury in this country and the study requires many patients because changes in response are small, but even a minor difference in the serious problem of central nervous injury could be important.

So my first question is: Does Dr. Young believe that glucose could help identify different groups of patients even within the same levels of the Glasgow coma scale? Second did he measure any other aspect of the stress response, such as norepinephrine, glucagon, and so on, to quantitate the stress response in perhaps a little more objective manner.

DR. DONALD BECKER (Los Angeles, California): The mechanically injured brain is susceptible to a second insult from hypoxia or ischemia from the hypotension that commonly occurs in brain-injured victims. The evidence is strong that a modest hypoxic insult and a modest hypotensive insult will result in a poorer outcome in patients with mechanical brain injury. The reason for this is because the mechanically traumatized brain is metabolically deranged and operates in a dysfunctional state. It may recover but if a normally innocuous second insult occurs, that insult can cause cells that could potentially recover to die. This has been confirmed in a number of animal experimental studies.

The mechanically traumatized brain is acidotic. This has been documented in both human and animal studies. Dr. Young has also pointed out that the human brain that has had a severe injury is acidotic and is continuously producing lactic acid. Dr. Young also noted that in ischemic brain injury, hyperglycemia exacerbates the extent and degree of damage to brain tissue.

Dr. Young do you think that hyperglycemia will cause a second insult to the injured brain? If so, should we maintain the patients in as normal a physiological state as possible as we are doing with the other parameters that we follow? Should we treat patients with hyperglycemia in the early period with insulin until the high blood sugar levels clear?

DR. JOHN S. SPRATT (Louisville, Kentucky): I just have a question. On my rotation with Henry Schwartz a long time ago he would never let us use very much glucose because he said it made the brain swell, and he said the reason was osmotic. I am just inquiring as to the current validity of just the osmotic effect of hyperglycemia independent of the pH effect in making the brain swell.

DR. JOSEPH M. CIVETTA (Miami, Florida): I just have one further question going beyond what Dr. Becker said. It is certainly tempting to correct hyperglycemia, but if the problem is the intracellular presence of glucose that leads to lactic acid production, might we run the danger of actually adding fuel to the fire and making the injury worse by correcting the hyperglycemia?

DR. BYRON YOUNG (Closing discussion): With regard to Dr. Collins' comment, I could not agree more. Neurosurgery has made tremendous progress in the last 10 years in the treatment of head injury. Most of this is due to the leadership of Dr. Becker showing that aggressive management of intracranial pressure (ICP) can improve the outcome of head-injured patients, but I agree with Dr. Collins that we are stymied at this point with managing ICP and now we need to go to the cellular level to try to improve outcome.

I do not believe that analysis of this will allow one to differentiate the degrees of severity of injury in a more precise manner than the Glasgow coma scale score, but I whole heartedly agree that we need better methods than the Glasgow coma scale score, and particularly the Glasgow outcome score, to measure our results. Again we did not measure any of the other parameters of the stress response.

To answer Dr. Becker's question, this study only looked at whether the patients were hyperglycemic when they were admitted, and we are looking only at the effect of stress, and we did not study the effect of the hyperglycemia on this.

I believe that we have not yet shown that hyperglycemia is damaging to the injured brain, but I only say this because there have not been animal or randomized clinical trials proving this. Our current practice is to maintain glucose levels less than 200 mg/% because I believe that the data that we have would indicate that this is the proper practice.

We do not have data to answer the question of what osmotic effect the various levels of glucose would have on intracranial pressure, and to answer Dr. Civetta's question, I do not believe that we would be making the injury worse by diminishing hyperglycemia. In fact I believe that would probably improve outcome, but perhaps the answer to this question is not the systematic management of glucose alone but the administration of other agents that will counteract the brain acidosis more directly.

Experience with the Use of High-Dose Interleukin-2 in the Treatment of 652 Cancer Patients

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We have administered 1039 courses of high-dose interleukin-2 (IL-2) to 652 cancer patients. Five hundred ninety-six patients had metastatic cancer that either had failed standard effective therapies or had disease for which no standard effective therapy existed, and 56 patients were treated in the absence of evaluable disease in the adjuvant setting. IL-2 was administered either alone (155 patients) or in conjunction with activated immune cells such as lymphokine activated killer (LAK) cells (214 patients) or tumor infiltrating lymphocytes (TIL) (66 patients), with other cytokines such as alpha interferon (a-IFN)(128 patients) or tumor necrosis factor (TNF)(38 patients), with monoclonal antibodies (32 patients), or with the chemotherapeutic agent cyclophosphamide (19 patients). Initial results with the treatment of high-dose IL-2 alone or in conjunction with LAK cells have indicated that objective regressions of cancer can be achieved in 20% to 35% of patients with selected advanced metastatic cancers. Although most responses have been seen in patients with metastatic renal cell cancer, melanoma, colorectal cancer, and non-Hodgkin's lymphoma, many histologic types of cancer have not been treated in significant numbers. These regressions can be durable; of 18 patients achieving a complete response, ten have not experienced recurrence at intervals from 18 to 52 months. Although combinations of IL-2 with TNF do not appear to result in increased responses, there is a suggestion in our initial phase I studies that the combination of a-IFN and IL-2 is more effective than the administration of cytokine alone and this combination deserves further study. Similarly the adoptive transfer of TIL in conjunction with IL-2 also appears to be more effective than the use of IL-2 alone. The toxic side effects in patients treated with high-dose IL-2 are presented and include malaise, nausea and vomiting, hypotension, fluid retention, and organ dysfunction. Treatment-related deaths were seen in 1% of all treatment courses and in 1.5% of patients. These studies demonstrate that a purely immunologic manipulation can mediate the regression of advanced cancers in selected patients and may provide a base for the development of practical, effective biologic treatments for some cancer patients.

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APPROXIMATELY ONE HALF OF all patients who develop cancer will eventually die of metastatic disease despite the best application of surgery, radiation therapy, and chemotherapy. Attempts to develop new approaches to the treatment of metastatic cancer by stimulating immune host defense reactions against the tumor have received substantial attention in recent years. The administration of high-dose interleukin-2 (IL-2), either alone or in conjunction with immune lymphoid cells can result in the regression of metastatic cancer in some patients and these results have spurred additional efforts to improve these treatments.[1–4]

Interleukin-2 is a 15.5 kD glycoprotein that plays a central role in immune regulation.[5] Activation of lymphocytes by specific antigen results in the generation of IL-2 receptors and the subsequent interaction of the lymphocyte with IL-2 leads to cell proliferation resulting in an immune response. IL-2 is only one of a multitude of hormones (cytokines) produced by lymphocytes and monocytes that result in the cascade of immune reactions.

In experimental animals, the administration of IL-2, either alone or in conjunction with other cytokines, monoclonal antibodies, chemotherapeutic agents, or immune lymphocytes, can mediate the rejection of cancers in lung, liver, and subcutaneous tissue.[6–8] The administration of IL-2 in conjunction with alpha-interferon (a-IFN) or tumor necrosis factor-alpha (TNF) resulted in synergistic antitumor activity compared to the use of IL-2 alone.[9,10] The administration of lymphokine activated killer (LAK) cells plus IL-2 similarly appeared more effective than IL-2 alone[11,12] and more recent studies showed that the administration of tumor infiltrating lymphocytes (TIL) plus IL-2 appeared to be 50 to 100 times more effective than the administration of LAK cells plus IL-2.[13]

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TREATMENT PROTOCOLS

	Day																	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
1) Interleukin-2 (I) alone	I	I	I	I	I									I	I	I	I	I
2) Interleukin-2 + Tumor Necrosis Factor (T)	T	T	T	I	I	I	I	I										
3) Interleukin-2 + alpha-Interferon (A)	I	I	I	I	I									I	I	I	I	I
	A	A	A	A	A									A	A	A	A	A
4) Interleukin-2 + Monoclonal Antibodies (M)	I	I	I	I	I									I	I	I	I	I
		M	M	M											M	M	M	
5) Interleukin-2 + Cyclophosphamide (C)		I	I	I	I	I												
	C																	
6) Interleukin-2 + Lymphokine Activated Killer (LAK) cells	I	I	I	I	I									I	I	I	I	I
														LAK	LAK		LAK	
		I	I	I	I	I								I	I	I	I	I
7) Interleukin-2 + Tumor Infiltrating Lymphocytes (TIL)	C																	
		TIL	TIL															

FIG. 1. General schemata for the use of high-dose Interleukin-2 in immunotherapy protocals.

These studies have lead to the development of a series of clinical trials to test the effectiveness of these immunotherapeutic approaches in patients with cancer. The current paper summarizes our results with the treatment of 652 patients who received 1039 courses of high-dose IL-2 given either alone or in combination with TNF, a-IFN, monoclonal antibodies, cyclophosphamide, LAK cells, or TIL.

Methods

Patients

The 652 patients in this trial had histologic confirmation of the diagnosis of cancer. Five hundred ninety-six patients had metastatic cancer that either had failed standard effective therapies or had disease for which no standard effective therapy existed. Fifty-six patients were treated in the absence of evaluable disease in the adjuvant setting. Thirty-six patients with malignant melanoma metastatic to draining lymph nodes were treated after resection of the draining lymph node group. Seventeen patients with colon cancer metastatic to the liver were treated after complete resection of hepatic metastases, and three patients with renal cell cancer metastatic to draining lymph nodes were treated after resection of the involved lymph nodes.

All patients with metastatic cancer had evaluable disease and had received no other therapy for their cancer for 1 month before entrance into the protocol or throughout the follow-up period. Patients were excluded from the protocol if they had major illnesses of the cardiovascular, respiratory, or renal systems and if they had any evidence of central nervous system metastases. For the past 3 years all patients older than 50 years entering the protocol underwent either a stress EKG or stress radionuclide ejection scan and patients with any evidence of ischemic heart disease were excluded from these protocols. Evaluation of all patients included CT or MRI scans of the brain, full lung tomograms, or CT scans of the chest, abdomen, and bones.

Treatment

The general outline of the treatment protocols is shown in Figure 1. In general patients received four to seven days of therapy followed by seven to ten days of rest and then an additional four to seven days of treatment. Responding patients, and in later protocols stable patients, generally received additional courses of treatment 2 to 3 months after the initiation of the first course of therapy. A brief summary of each of the individual protocols follows.

IL-2 alone. Recombinant IL-2 was administered intravenously in bolus doses every eight hours.[14] IL-2 (supplied by the Cetus Corporation, Emeryville, CA) was administered at doses of 100,000 U/kg, although fewer patients received doses between 10,000 and 30,000 U/kg. IL-2 (supplied by Hoffman-LaRoche, Nutley, NJ) was administered at doses of 1,000,000 to 6,000,000 U/m^2. Patients received IL-2 for up to five days followed by a seven to ten day rest followed by five more days of treatment.

IL-2 plus Tumor Necrosis Factor-Alpha (TNF). IL-2 and TNF were supplied by the Cetus Corporation (Emeryville, CA). TNF was administered as an intravenous bolus dose once a day on days 1, 2, and 3, followed by IL-2 starting on day 4 every eight hours for up to five days. IL-2 doses varied from 30,000 to 100,000 U/kg and the doses of TNF varied from 50 to 350 ug/m^2. Up to eight patients were entered into each dose schedule to determine the maximum tolerated doses of the combination of IL-2 and TNF.

IL-2 plus Alpha-Interferon (a-IFN). IL-2 and a-IFN were supplied by Hoffman-LaRoche Inc. (Nutley, NJ). IL-2 and a-IFN were administered concurrently, intravenously, every eight hours for up to five days, followed by a seven-to-ten day rest, followed by a second cycle of treatment. As detailed later in some escalating dose regimens, the a-IFN was given once a day. The dose of IL-2 in this procotol varied from 1,000,000 to 6,000,000 U/m^2 and the dose of a-IFN varied from 3,000,000 to 6,000,000 U/m^2.

IL-2 plus monoclonal antibodies (MoAb). IL-2 was administered as in the protocol using IL-2 alone. However monoclonal antibody directed against either melanoma or colorectal cancer antigens were administered intravenously, generally twice daily, during the course of IL-2 treatment.

IL-2 plus cyclophosphamide. A single dose of cyclophosphamide ranging from 10 to 50 mg/kg was administered intravenously after a 12-hour period of intravenous hydration. Twenty-four to 36 hours after the cyclophosphamide, IL-2 administration began as in the protocol using IL-2 alone.

IL-2 plus lymphokine activated killer (LAK) cells. This treatment regimen has been extensively described elsewhere.[1,3,15] Up to five days of IL-2 administration preceded four to five days of leukapheresis to obtain peripheral lymphocytes. LAK cells were generated in culture and reinfused during the second cycle of treatment along with the concomitant administration of IL-2 as in the protocol using IL-2 alone.

IL-2 plus tumor infiltrating lymphocytes (TIL). This protocol has been described in detail elsewhere.[4,16] Patients received a single dose of cyclophosphamide, generally at 25 mg/kg, followed 24 to 36 hours later by the administration of TIL and the concomitant administration of IL-2 as in the protocol using IL-2 alone.

Evaluation of Response to Treatment

A response was considered to be complete if all measurable tumor disappeared. A partial response was defined as a 50% decrease in the sum of the product of the longest perpendicular diameters of all lesions, lasting at least 1 month, without increase in any tumor or the appearance of any new tumor. Any patient who did not achieve at least a partial response is considered a nonresponder in this analysis. The response durations were computed from the time of the first dose of IL-2 until disease progression.

Results

Between November 1984 and March 1989, 652 patients with cancer underwent treatment with 1039 courses of immunotherapy using high-dose IL-2. Eleven of these patients were treated in two separate protocols and each protocol was evaluated separately. Five hundred ninety-six patients had metastatic cancer and 56 patients were treated after resection of all disease in the adjuvant setting.

Characteristics of these patients are shown in Table 1. Most patients were between the ages of 30 and 60 and all but 16 patients had received previous treatment for their cancer. Six hundred seven patients had undergone surgical therapy, 183 had received chemotherapy, and 120 had received radiation therapy. Two hundred seventy-four patients had received at least two forms of treatment and 96 patients had received three treatment modalities. The majority of the patients treated in these protocols had malignant melanoma or metastatic renal cell cancer; these two diagnoses comprised 477 of the 652 patients. Ninety-nine patients had colorectal cancer, 21 had metastatic breast cancer, and 18 had non-Hodgkin's lymphomas. Less than ten patients with any other histology were treated. Most patients had good performance status, which was required for entrance into these clinical protocols.

All patients in these studies were accrued as of March 1989 and follow-up is included to that date as well. Response data is presented only for those patients having at least 2 months of follow-up after the last dose of immunotherapy.

The characteristics of the immunotherapy treatments are shown in Table 2. Six hundred seventy-eight of the 1039 treatment courses were given at a dose of 100,000 U/kg every eight hours, which is the maximum tolerated dose of IL-2. Few patients can receive more than 15 doses at this dose level. Doses of IL-2 and the cumulative IL-2 dose for each of the protocols are shown in Table 2. The number of patients receiving LAK cells or TIL in each protocol and the number of cells received is also shown.

Our initial studies dealt with the administration of high-dose IL-2 given either alone or in conjunction with the adoptive transfer of LAK cells.[1-3] The results of these protocols, presented in Tables 3 and 4, of the treatment of 307 patients represents an update of previously published results on 212 patients[8] with an additional 20 months of follow-up. The results of patients treated with IL-2 alone include all patients with the exception of four who died of therapy-related complications and 21 who were treated in the absence of evaluable disease in the adjuvant setting (Table 3). Of these 130 patients, the only two diseases with appreciable numbers of patients are renal cell cancer and melanoma and the objective response rates in these diseases were 22% and 24%, respectively. No objective responses were seen in 12 colorectal cancer patients or 11 patients with non-Hodgkin's lymphoma. No more than three other patients with any single histology were treated, and thus no comments could be made about the effectiveness of this therapy in patients with other histologic types of cancer.

A similar update of our treatment results in 177 patients with advanced cancer treated with LAK cells and IL-2 is

TABLE 1. *Characteristics of Patients Receiving Immunotherapy*

Interluekin-2 Plus		Alone	TNF	a-IFN	MoAB	CYT	LAK	TIL	Total
		Number of Patients							
Total		155	38	128	32	19	214	66	652*
Sex	Male	91	21	83	19	11	137	40	402
	Female	64	17	45	13	8	77	26	250
Age	11–20	3	2	1	—	—	3	—	9
	21–30	10	4	6	—	4	22	11	57
	31–40	34	9	19	8	7	42	17	136
	41–50	54	11	42	7	2	63	16	195
	51–60	39	8	42	13	4	61	20	187
	61–70	15	4	18	4	2	23	2	68
Previous Treatment	None	4	—	7	—	—	4	1	16
	Surgery	139	38	119	31	19	199	62	607
	Chemotherapy	48	9	27	17	7	64	11	183
	Radiotherapy	27	10	21	4	2	45	11	120
	Hormonal	12	1	3	1	—	7	2	26
	Immunotherapy	20	5	13	4	4	27	17	90
	Any 2 or more	64	18	49	19	10	90	24	274
	Any 3 or more	25	5	12	5	3	35	11	96
Diagnosis	Melanoma	60	15	53	12	13	66	51	270
	Renal cell	58	10	51	—	3	74	11	207
	Colorectal	14	7	10	20	—	46	2	99
	Breast	4	5	5	—	3	2	2	21
	NH lymphoma	11	—	—	—	—	7	—	18
	NSC lung	1	—	1	—	—	5	—	7
	ST sarcoma	1	—	2	—	—	4	—	7
	Brain	2	—	—	—	—	1	—	3
	Esophageal	—	—	1	—	—	1	—	2
	Gastrinoma	—	1	—	—	—	1	—	2
	Liver	2	—	—	—	—	—	—	2
	Ovarian	1	—	—	—	—	1	—	2
	Prostate	—	—	2	—	—	—	—	2
	Small bowel	—	—	2	—	—	—	—	2
	Testicular	—	—	1	—	—	1	—	2
	Ewing's	—	—	—	—	—	1	—	1
	Hodgkin's	—	—	—	—	—	1	—	1
	Osteosarcoma	—	—	—	—	—	1	—	1
	Pancreatic	1	—	—	—	—	—	—	1
	Thyroid	—	—	—	—	—	1	—	1
	Unknown primary	—	—	—	—	—	1	—	1
Performance†	0	109	34	112	26	11	132	53	477
	1	36	3	13	3	6	60	11	132
	2	8	1	3	3	1	21	1	38
	3	2	—	—	—	1	1	1	5

* Eleven patients are in two protocols.

† Eastern Cooperative Oncology Group criteria.

presented in Table 4. This represents all of our treated patients except one lost to follow-up, one who died of therapy related complications, and 35 who were treated without evidence of disease in the adjuvant setting. Of 72 patients with renal cell cancer and 48 patients with metastatic melanoma, response rates were 35% and 21%, respectively. One complete response and four partial responses were seen in 30 patients (17%) with metastatic colorectal cancer and four objective responses were seen in seven patients with non-Hodgkin's lymphoma (57%). Too few patients with other histologic types of cancer were treated to draw any conclusions about efficacy in other histologic types of cancer.

Tumor responses were seen in these patients at a variety of sites including lung, liver, bone, subcutaneous tissue, skin, and circulating tumor cells. When tumor at a single site regressed, regression generally occurred at all sites. Mixed responses were rare and were categorized as nonresponses. Maximum follow-up in these patients now extends to 52 months. The duration of responses as of March 1989 in patients treated with IL-2 and LAK/IL-2 is shown in Table 5. The limited duration since the onset of these

TABLE 2. *Characteristics of the Immunotherapy Treatments*

Interleukin-2 Plus		Alone	TNF	a-IFN	MoAB	CYT	LAK	TIL	Total
Number of Patients		155	38	128	32	19	214	66	652*
Number of Courses		236	85	210	35	30	348	95	1039
Dose IL-2	100	212	22	—	31	30	297	86	678
(CC: U/kg × 10^{-3})	60	—	21	—	—	—	—	—	21
	30	7	42	—	4	—	21	8	82
	20	4	—	—	—	—	9	—	13
	10	1	—	—	—	—	21	1	23
(HL: U/m^2 × 10^{-6})	6.0	7	—	12	—	—	—	—	19
	4.5	5	—	104	—	—	—	—	109
	3.0	—	—	85	—	—	—	—	85
	1.0	—	—	9	—	—	—	—	9
Number IL-2 doses	1–10	52	50	25	10	11	30	57	235
	11–20	129	35	137	22	19	235	33	610
	21–30	51	—	48	3	—	54	5	161
	31–40	4	—	—	—	—	12	—	16
	41+	—	—	—	—	—	17	—	17
Cumulative IL-2 dose	1–500	17	52	—	2	—	18	25	114
(CC: U/kg × 10^{-3})	501–1000	39	21	—	11	11	54	34	170
	1001–2000	122	12	—	21	19	238	32	444
	2001–3000	42	—	—	1	—	31	4	78
	3001–4000	4	—	—	—	—	6	—	10
	4001–5000	—	—	—	—	—	1	—	1
(HL: U/m^2 × 10^{-6})	1–50	4	—	65	—	—	—	—	69
	51–100	5	—	134	—	—	—	—	139
	101–150	3	—	11	—	—	—	—	14
Number of cell doses	1–5	7	—	—	2	—	306	85	400
	6–10	—	—	—	—	—	34	—	34
	11–14	—	—	—	—	—	3	—	3
Cumulative cells	0.1–5.0	—	—	—	—	—	41	11	52
(×10^{-10}	5.1–10.0	1	—	—	—	—	139	16	156
	10.1–15.0	3	—	—	—	—	101	11	115
	15.1+	3	—	—	2	—	62	47	114

* Eleven patients are in two protocols.

clinical efforts precludes definitive comments about the duration of responses, although it is interesting that 14 of the responding patients have remained in sustained response for more than two years. Of 18 patients in complete remission, ten remain in complete remission at 18 to 52 months. It thus appears that at least some patients with

TABLE 3. *Results of Immunotherapy in Patients with Advanced Cancer (March 1989)*

	Treatment with IL-2 (number of patients)			
Cancer Diagnosis	Evaluable*	CR	PR	CR + PR (%)
Renal	54	4	8	22
Melanoma	42	0	10	24
Colorectal	12	0	0	—
Non Hodgkin's Lymphoma	11	0	0	—
Breast	3	0	0	—
Other†	8	0	0	—
Total	130	4	18	17

* Includes all treated patients except four that died of therapy and 21 treated in adjuvant setting.

† Two patients each with hepatoma and brain cancer; one each with sarcoma, lung, ovary and pancreas.

TABLE 4. *Results of Immunotherapy in Patients with Advanced Cancer (March 1989)*

	Treatment with LAK/IL-2 (number of patients)			
Cancer Diagnosis	Evaluable*	CR	PR	CR + PR (%)
Renal	72	8	17	35
Melanoma	48	4	6	21
Colorectal	30	1	4	17
Non-Hodgkin's lymphoma	7	1	3	57
Sarcoma	6	0	0	—
Lung	5	0	0	—
Other†	9	0	0	—
Total	177	14	30	25

* Includes all treated patients except one lost to follow-up, one died of therapy and 35 treated in adjuvant setting.

† One patient each with cancer of breast, brain, esophagus, ovary, testes, thyroid, gastrinoma, Hodgkin's, unknown primary.

TABLE 5. *Duration of Responses (as of March 1989) Expressed in Months*

	LAK/IL-2		IL-2	
Diagnosis	CR	PR	CR	PR
Renal	30+, 27+, 23+, 15, 13, 11, 9, 6	36+, 21+, 19, 13, 11, 11, 9, 7, 7, 6, 6, 6, 6, 3, 2, 1, 1	34+, 28+, 27+, 25+	27+, 27+, 25+, 21+, 21+, 19+, 15+, 3+
Melanoma	52+, 32+, 18+, 13	30+, 6, 6, 3, 2, 2	—	41+, 15, 12, 11, 10, 8, 7, 5, 3, 2
Colorectal	21	11, 6, 6, 2	—	—
Non-Hodgkin's lymphoma	10	31+, 20, 8+	—	—

Of 18 patients with complete remission, 10 remain in CR at 18 to 52 months.

metastatic cancer experience durable complete and partial remissions when treated with this form of immunotherapy.

As patients accrued in protocols containing IL-2 and IL-2 plus LAK cells, we explored the administration of combinations of cytokines in murine models. Substantial synergistic effects were seen in models of established murine tumors using the combinations of TNF with IL-2 and a-IFN with IL-2.[9,10] In these murine models a direct relationship existed between antitumor response and the amount of both IL-2 and either TNF or a-IFN administered.

We thus began phase I clinical trials in patients with advanced cancer to seek the maximum tolerated dose of the combined administration of either IL-2 and TNF or IL-2 and a-IFN. An example of the design of the IL-2/TNF trial is shown in Table 6. Three to eight patients were entered into an escalating dose trial in which the IL-2 was varied between 30,000 and 100,000 U/kg q8h after three daily doses of TNF given at doses of 50 to 300 ug/m^2. A single patient was treated at 350 ug/m^2, although this dose proved to be intolerable due to hypotensive side effects. It thus appears that the maximum tolerated dose of both IL-2 and TNF was 100,000 U/kg of IL-2 q8h for up to five days after three daily doses of TNF at 300 ug/m^2. The response of patients in this phase I trial is shown in Tables 6 and 7. One complete response in a patient with metastatic melanoma and three partial responses were seen in patients with metastatic renal cell cancer. The complete responder is still in remission at 14 months and one of the partial responses is continuing at 13 months; two other partial responses progressed at 5 and 7 months, respectively (Table 6). This response rate is not different from that expected from the use of IL-2 alone.

A similar escalating dose trial was conducted using the combination of IL-2 and a-IFN in patients with advanced cancer. This trial, which used Hoffman-LaRoche IL-2 (compared to IL-2 from Cetus Corporation used in previous trials) involved escalating doses of IL-2 and a-IFN. A-IFN was administered at a dose of 3,000,000 U/m^2 q8h concurrent with the administration of 1,000,000 U/m^2 of IL-2 q8h (in six patients), 3,000,000 U/m^2 q8h (in 32 patients) and 4,500,000 U/m^2 q8h (in 26 patients). In addition 30 patients received a-IFN at a dose of 6,000,000 U/m^2 q8h with the concurrent administration of IL-2 at 4,500,000 U/m^2 q8h, and 21 additional patients received 6,000,000 U/m^2 of a-IFN once a day along with the administration of 6,000,000 U/m^2 of IL-2 q8h. Patients received two cycles of treatment, as shown in Figure 1, to a maximum of 15 doses per cycle. Preliminary results of treatment in this protocol are shown in Table 7. Although follow-up is short, it appears that increased response rates are seen in patients accrued at higher doses of a-IFN and IL-2 with response rates at 41% in patients with renal cancer and melanoma at the highest dose escalation. We have not yet reached the maximum tolerated doses in this protocol and accrual is continuing.

In mice bearing advanced tumors we showed that the administration of high-dose IL-2, in conjunction with cyclophosphamide, mediated more potent antitumor responses than treatments with IL-2 alone or cyclophosphamide alone.[17] We thus conducted a phase I study using escalating doses of cyclophosphamide from 10 mg/kg to 50 mg/kg in conjunction with high-dose IL-2. The results in 19 patients treated in this phase I protocol are shown in Table 7. Only two partial responses were seen in patients with melanoma and although the number of patients treated was small, it does not appear that higher response rates are seen compared to the use of IL-2 alone. It should be noted, however, that the three tumor types treated in this study, renal cell cancer, melanoma, and patients with heavily pretreated breast cancer, are not responsive to cyclophosphamide.

TABLE 6. *IL-2/TNF Protocol*

Dose			
IL-2 $(\times 10^{-5}\ \mu/\text{Kg})$	TNF (μg/m^2)	Number of Patients	Responses
30	50	3	1 PR (5 months)
30	100	3	
30	150	3	1 PR (7 months)
30	200	3	1 CR (14+ months)
30	300	5	
60	200	3	1 PR (13+ months)
60	250	3	
60	300	3	
100	300	8	
100	350	1	
Total		38	4

TABLE 7. *Results of Immunotherapy in Patients with Advanced Cancer (accrued by March 1989)*

	(Number of Patients)								
	Cy/IL-2			TNF/IL-2			aIFN/IL-2		
Diagnosis	Total Evaluable	CR	PR	Total Evaluable*	CR	PR	Total Evaluable†	CR	PR
Renal	3	0	0	10	0	3	46	4	11
Melanoma	13	0	2	15	1	0	44	3	13
Colorectal				6	0	0	10	0	1
Non-Hodgkin's lymphoma									
Sarcoma							1	0	0
Lung adenocarcinoma							1	0	0
Breast	3	0	0	5	0	0	5	0	0
Esophageal							1	0	0
Testicular							1	0	0
Hepatoma							1	0	0
Small intestine							1	0	0
Gastrinoma				1	0	0			
Prostate									
Total	19	0	2	37	1	3	113	7	25

* Includes all treated patients except for one with colorectal cancer found to have a simultaneous non-Hodgkin's lymphoma and received chemotherapy.

† Excludes patients with less than two months follow-up.

Similarly animal models have shown that the combination of specific monoclonal antibodies plus high-dose IL-2 can mediate synergistic antitumor effects.[18] These studies led us to design escalating dose phase I studies of the use of monoclonal antibodies and IL-2 in cancer patients. These studies are currently in their escalating dose phase and no antitumor responses have been seen.

Murine tumor models have indicated that the administration of TIL in conjunction with IL-2 is 50 to 100 times more potent than is the administration of LAK cells and IL-2 in mediating the regression of a variety of established murine cancers.[13] We have recently reported the results of treatment with TIL and IL-2 in patients with malignant melanoma.[4] In preliminary studies it appears that approximately 50% of patients with metastatic melanoma show objective responses to this latter treatment. This preliminary work has recently been published and will not be considered further here, although these patients are considered in the overall evaluation of the toxicity of treatment.

Toxicity of Immunotherapies Containing High-Dose IL-2

The toxicities associated with the administration of high-dose IL-2 are directly related to the dose of IL-2 administered. We have previously reported the toxicity of high-dose IL-2 used either alone or in conjunction with LAK cells in 212 patients with advanced cancer.[3,8] In this paper we update this data to report the toxicity of the administration of high-dose IL-2 either alone or in combination with other cytokines, monoclonal antibodies, cyclophosphamide, or immune lymphocytes in 652 patients receiving 1039 courses of treatment (Table 8). This tabulation includes all patients we have treated, including those with metastatic cancer, and the 56 patients treated in the absence of evaluable disease in the adjuvant setting. All patients received high-dose IL-2 and the contribution to toxicity of the additional agents varied somewhat depending on the dose of the additional agent administered. Systemic symptoms were common and many patients experienced nausea and vomiting, diarrhea, and malaise during therapy. All patients received acetaminophen, indomethacin, and ranitidine to allievate these symptoms. Transient organ dysfunctions were common and elevations of bilirubin and creatinine were often found. These elevations returned to normal with a median of four days after discontinuing treatment.

Many of the side effects associated with high-dose IL-2 treatment are similar to those seen in patients with sepsis, including a decrease in peripheral vascular resistance, an increase in cardiac index, tachycardia, oliguria, and hypotention. A capillary permeability increase led to fluid extravasation into soft tissues and a weight gain of more than 5% of the total body weight in most patients. Vasopressors were used early in the treatment course to reduce the fluid requirement necessary to maintain urine output and blood pressure.

Ten patients died of therapy-related complications, which represented 1% of all treatment courses and 1.5% of all patients.

Discussion

In this paper we present our efforts exploring the use of high-dose IL-2 in conjunction with other immunotherapeutic manipulations to develop effective immunother-

TABLE 8. *Toxicity of Treatment with Interleukin-2*

Interleukin-2 Plus	Alone	TNF	a-IFN	MoAB	CYT	LAK	TIL	Total
Number of Patients	155	38	128	32	19	214	66	652*
Number of Courses	236	85	210	35	30	348	95	1039
Chills	75	16	68	8	8	191	33	399
Pruritus	53	9	26	2	2	82	6	180
Necrosis	3	—	2	—	—	—	—	5
Anaphylaxis	—	—	—	1	—	—	—	1
Mucositis (requiring liquid diet)	6	1	7	—	2	12	2	30
Alimentation not possible	1	—	1	—	—	2	—	4
Nausea and vomiting	162	42	117	14	20	263	48	666
Diarrhea	144	38	98	15	13	250	38	596
Hyperbilirubinemia (maximum/mg %)								
2.1–6.0	126	49	97	21	18	190	46	547
6.1–10.0	49	3	12	8	9	72	26	179
10.1+	26	1	4	3	1	40	8	83
Oliguria								
<80 ml/8 hours	81	37	67	14	9	114	25	347
<240 ml/24 hours	19		2	3	1	12	5	42
Weight gain (% body weight)								
0.0–5.0	106	23	65	8	9	117	49	377
5.1–10.0	78	41	111	22	10	148	26	436
10.1–15.0	43	17	26	3	9	62	15	175
15.1–20.0	7	3	8	1	1	15	3	38
20.1+	2	1		1	1	6	2	13
Elevated creatinine (maximum/mg %)								
2.1–6.0	148	43	121	20	14	237	54	637
6.1–10.0	21	1	14	3	—	34	12	85
10.1+	5	—	1	1	—	2	1	10
Hematuria (gross)	—	—	—	—	—	2	—	2
Edema (symptomatic nerve or vessel compression)	4	—	6	—	—	7	—	17
Tissue ischemia	—	—	—	—	1	1	—	2
Resp. distress:								
not intubated	17	1	9	4	1	28	7	67
intubated	15	—	6	3	—	12	5	41
Bronchospasm	2	—	2	—	1	4	—	9
Pleural effusion (requiring thoracentesis)	4	1	—	1	2	8	1	17
Somnolence	29	2	22	6	2	45	8	114
Coma	9	1	8	—	2	8	5	33
Disorientation	52	3	50	7	4	89	10	215
Hypotension (requiring pressors)	119	16	40	17	12	259	45	508
Angina	5	1	8	—	—	8	—	22
Myocardial infarction	4	—	1	—	—	1	—	6
Arrythmias	15	2	13	3	—	39	6	78
Anemia requiring transfusion (number units transfused)								
1–15	77	16	53	9	6	176	40	377
6–10	22	1	5	3	2	53	9	95
11–15	4	—	1	—	—	15	4	24
16+	1	—	1	—	—	11	1	14
Thrombocytopenia (minimum/mm^3)								
<20,000	28	1	2	4	6	71	19	131
20,001–60,000	82	11	62	14	12	150	30	361
60,001–100,000	53	36	76	11	8	79	22	285
Central line sepsis	13	—	7	1	4	36	2	63
Death	4	—	1	—	—	3	2	10

* Eleven patients are in two protocols.

apies for the treatment of patients with cancer. Results of the use of high-dose IL-2 alone or in conjunction with LAK cells demonstrate that a purely immunologic manipulation is capable of mediating the regression of established cancer in humans. Although the earlier use of interferon to mediate tumor regression may have an immunologic basis, the direct antiproliferative effects of the interferons suggest that these agents may be acting directly on the tumor rather than stimulating the host reaction to the tumor.[19]

The treatment of patients with advanced cancer using IL-2 and LAK cells can result in durable clinical remissions even in patients with advanced tumor burdens (Table 5). In experimental animal models the use of IL-2 alone can mediate tumor regression, although the administration of LAK cells results in a more substantial antitumor effect at all doses of IL-2 administered.[11,12] We have recently completed a prospective randomized trial of 181 patients randomized to receive either IL-2 alone or IL-2 plus LAK cells. Although the overall response rates are similar in these two regimens, the incidence of complete responses is greater in patients who received LAK cells plus IL-2 ($p = 0.04$). Follow-up is short and further evaluation of this question is in progress.

In the development of these immunotherapies, experiments in animal models have played an important role in predicting the appropriate design of clinical trials in humans with advanced cancer. These animal models revealed a substantial therapeutic synergy between IL-2 and TNF and between IL-2 and a-IFN.[9,10] In the phase I study of TNF plus IL-2, we have reached the limiting toxicity of the combined administration of these agents and we have not seen a suggestion of increased activity due to the combination. Clinical trials of TNF alone in cancer patients have yielded disappointing results and the reason for the activity of TNF in animal models but not in humans is not well understood.[20] In our initial phase I efforts it does appear that a-IFN and IL-2 may have additive or synergistic activity in patients with advanced cancer, although additional patients must be entered at the maximum tolerated doses to draw definitive conclusions.

In addition to the use of combination cytokines, animal models have indicated that the combined use of IL-2 with chemotherapeutic agents such as cyclophosphamide,[17] or with monoclonal antibodies directed against antigens on the tumor cell surface may synergize with IL-2 administration.[18] These animal models included tumors that were sensitive to cyclophosphamide in contrast to the human tumors treated in our patients who were either nonresponsive to chemotherapy or failed available chemotherapies. We have not seen a suggestion of combined therapeutic activity in combining cyclophosphamide and IL-2 in these patients, although it is possible that a synergy would be seen if an effective chemotherapy were used. Ongoing trials in the Surgery Branch, NCI, are exploring the use of 5-fluorouracil plus leucovorin in conjunction with IL-2 or monoclonal antibodies plus and IL-2 in the treatment of patients with metastatic colorectal cancer.

We have sought means to identify cells with greater therapeutic potency for the adoptive immunotherapy of patients with advanced cancer, and a recent clinical trial has suggested that TIL may be more effective than LAK cells in the treatment of patients with metastatic melanoma.[4] These TIL, which are T cells, in contrast to LAK, which are null cells, often exhibit unique lytic activity, *in vitro*, to autologous melanoma cells and not to other normal cells from that patient or to allogeneic melanoma cells.[16,21] The *in vitro* activity of these TIL provides the best evidence now available that at least some patients with growing cancers can mount immune reactions to their malignancy. Continued work with these TIL is in progress.

The use of high-dose IL-2 alone or in combination regimens provided us with the opportunity to analyze the toxic side effects of this treatment in 652 patients who received 1039 courses of immunotherapy. The major side effects of IL-2 result from its tendency to induce a capillary leak syndrome, from the growth of lymphocytes in visceral organs throughout the body, and from stimulation of the secretion of other cytokines by cells of the immune system.[22-25] Many of the side effects of IL-2 resemble those seen in patients with septic shock and it is possible that some of these side effects are due to the stimulation by IL-2 of the secretion of TNF by mononuclear cells. These side effects are quite transient and reverse readily after IL-2 therapy is discontinued.

Since the beginning of our experience with high-dose IL-2, 1.5% of patients died due to treatment-related causes. This rate is substantially lower than that associated with the use of virtually any combination chemotherapy in standard use in patients with advanced cancer. Thus although the toxicity of the administration of IL-2 can be severe, it is readily managed in the great majority of patients and high-dose IL-2 either alone or in combination with other agents can be safely administered. Supporting this contention is the fact that one treatment related fatality was seen in 94 patients treated in a multi-institution trial using high-dose IL-2 and LAK cells and by the safe use of LAK/IL-2 in other reported trials.[26-29]

Current clinical efforts are being devoted to a continued exploration of combination cytokine therapy and the use of immunotherapy in patients with decreased tumor burdens. In these latter efforts immunotherapy is being used in combination with surgery, radiation therapy, and chemotherapy. One approach with substantial promise for improving the effectiveness of adoptive cellular therapy is our ability to modify TIL by gene insertion. Traffic studies with Indium^{111}-labeled TIL have indicated that these TIL can "home" to tumor deposits and thus TIL might represent ideal packets to deliver toxic substances directly to the tumor site.[30] We have recently received authorization from the Recombinant DNA Advisory Committee, the National Institutes of Health, and the Food and Drug Administration to perform gene transfer studies in humans using TIL. In initial clinical trials, genes coding for neomycin resistance will be transduced into TIL using retroviral vectors to enable studies of the long-term distribution and survival of TIL. Future experiments are planned to explore the therapeutic potency of TIL modified by genes coding for other cytokines such and TNF, a-IFN, and perhaps IL-2 itself.

The use of high-dose IL-2 in the treatment of patients with cancer administered either alone or in combination with other agents represents an approach to the biologic therapy of patients with advanced cancer that is in the early stages of its development and, we hope, may provide a base for the development of practical effective therapies for the treatment of patients with cancer.

Acknowledgments

This clinical trial involved the efforts of a number of dedicated people. We particularly acknowledge the outstanding help of the data managers, Melissa Corbitt and Allison McMullen, and the dedicated nurses of the 2 East Surgical Unit and the 2J Surgical Intensive Care Unit of the Clinical Center, National Institutes of Health, who provided these patients with excellent and compassionate care.

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DISCUSSION

DR. CHARLES M. BALCH (Houston, Texas): Dr. Rosenberg has made major contributions in this important and evolving area of research involving biologic therapy. His research represents a blend of both excellent preclinical models and well-controlled clinical trials. I have a few comments relevant to the lymphokines he discussed today and would like to ask two questions.

(Slide) The battlefield for host–tumor relationships is within the tumor, and here again Dr. Rosenberg has done pioneering work in examining TIL and exploring their use as a treatment strategy. There is a profound defect of the lymphocytes that are recovered from such cancer as melanoma and renal cell carcinoma in that they cannot bind or kill autologous tumor cells. However this deficit can be corrected *in vitro* by adding Interleukin-2, and Dr. Rosenberg proposes that at least in some patients you can augment cellular immune responses *in vivo* as well as by administering Interleukin-2 in combination with other lymphokines.

We have studied these TIL extensively and found an extraordinary diversity of the immune responses. However some patterns emerge as shown in this study of more than 120 human tumors in which we classified the subtypes of lymphocytes that emigrated into the tumor and their growth rate with Interleukin-2. In melanoma most of these cells are T-cells with a cytotoxic phenotype ($CD8^+$). There are almost no NK cells. Renal cell carcinomas, on the other hand, have both T-cell subsets and NK-cells, as do sarcomas. Breast cancers and colon cancers are different yet again. The cytotoxic capacity of these cells is also quite different among various human cancers. Thus TIL from distant metastatic melanoma has an efficient level of cytotoxicity that is restricted to the patient's own tumor (*i.e.*, they cannot kill allogeneic cells). TIL from lymph node metastases from melanomas are very inefficient cytotoxic effector cells. TIL from renal cell carcinomas are different from those in melanomas because these lymphocytes have the capacity to kill both autologous and allogenic tumor target cells.

Because biologic therapy is an indirect approach to eliminate cancers by augmenting an immune rejection response, one would expect that there would be some variations from tumor to tumor and site to site, and would also emphasize an important part of Dr. Rosenberg's treatment strategy in that he used multiagent immunotherapy using agents with different mechanisms of action.

I would like to ask two questions. First do you have any idea about the nature of the functional defect of these tumor-infiltrating lymphocytes that appear to be overcome *in vitro* by adding back pharmacologic doses of Interleukin-2? Second what is the relative contribution of the expanded lymphocytes that are included in the Interleukin-2 regimens? That is how do you know that the TIL or LAK cells are contributing significantly to these tumor responses *in vivo*? Do you have data now from your studies, either by trafficking or clinical trials, showing the relative contribution of adoptive immunotherapy compared to the therapeutic effect of using the lymphokines alone?

DR. DONALD L. MORTON (Los Angeles, California): To Dr. Rosenberg must go the credit for ushering in the modern era of immunotherapy with cytokines, in combination with adoptive immunotherapy with lympoid cells. I admire Dr. Rosenberg, not only for his scientific advances, but especially for his tenacity and hard work in dealing with 652 critically ill patients with hopeless malignancy who have undergone the toxicity he has described with IL-2. The response rates of 21% to 35% in disseminated melanoma and renal cell cancer are impressive. The even higher response rates of 35% to 50% with alpha interferon and IL-2 and TIL-IL-2 are even more significant when one considers that these tumors are refractory to chemotherapy.

It is perhaps significant that these responses are all or none, which is different from chemotherapy in which there are often only partial responses in some metastatic sites. I want to ask Dr. Rosenberg two questions: Does he have an explanation for this all-or-none phenomenon, and does he know the target structure to which the IL-2 LAK cells are directed?

Our own work has concentrated on active specific immunotherapy with tumor cell vaccines, and I thought this might be a chance to give the Association a brief update. We have used a whole cell vaccine composed of three allogeneic melanoma cell lines irradiated to 10,000 rads and administered intradermally. Low-dose cyclophosphamide has been used as an immunomodulator and compared this with tumor cell vaccine alone. The early results in the 300 mg/M^2 dosage shows no difference between tumor cell vaccine alone and tumor cell vaccine with cyclophosphamide.

However if one compares the results we have seen with vaccine immunotherapy with those previously seen with chemotherapy in disseminated melanoma, we see that the patients receiving vaccine with or without cyclophosphamide do significantly better. The median survival for chemotherapy is 6 to 9 months *versus* 16 months for immunotherapy; the 40-month survival for immunotherapy is 30% *versus* 5% for chemotherapy.

We began to see a rise in antibody titer to one or more of the seven melanoma-associated cell surface antigens 4 to 8 weeks after the start of immunotherapy. Regression of evaluable disease begins at about 3 months.

(Slide) This is a patient with extensive recurrent melanoma over the ear, face, and neck, refractory to chemotherapy and radiation therapy treated with this vaccine. After 4 months, partial regression is observed. After 10 months it is almost complete, except for some small, residual disease on the cheek, which is completely gone at 19 months. This patient is free of disease at 36 months.

Of 25 patients treated with evaluable disease who were treated, we have had two complete regressions and an overall response rate of 25%. It is interesting that the responses we see with active specific immunotherapy are slower in their evolution, but are of more durable duration than the responses we see with chemotherapy.

DR. JEROME J. DECOSSE (New York, New York): May I ask Dr. Rosenberg a point of clarification. Were any of the patients described in your talk also treated with either radiation therapy or chemotherapy and can you exclude an effect of these other modalities?

DR. JONATHAN L. MEAKINS (Montreal, Canada): Last year Dr. Wilmore presented a paper that showed that ibuprofin could control some of the symptoms associated with IL-2, and the question was raised at that time whether that would affect any of the antitumor effects of LAK cells and IL-2 or other cytokines.

I wonder if Dr. Rosenberg could tell us whether he has been looking at this. It may have very real implications for the acceptability of this form of therapy as well as its more general applicability in other than very highly specialized centers.

DR. THOMAS C. MOORE (Los Angeles, California): Dr. Rosenberg's report of his innovative work with lymphokines alone and in combination and his use of tumor-infiltrating lymphocytes is most impressive. It is not unreasonable to assume that these lymphocytes are in tumors for a reason and Dr. Rosenberg and his associate have made important advances in exploring this intriguing potential.

I wish to ask Dr. Rosenberg if he and his associates have considered the involvement and use of other types of soluble mediators such as potent vasoactive neurotransmitter substances? I am thinking of immunostimulative substances such as bradykinin and substance P, which are involved also in inflammation and pain transmission.

We have observed and reported that intralesional administration of bradykinin in hamsters has produced malignant tumor growth slowing and regression. Bradykinin *in vitro* has increased the antitumor cell cytolytic activity of spleen cells from tumor-bearing animals whose tumor growth has been slowed or stopped by intralesional administration of bradykinin.

Professor Robert Fauve, of the Pasteur Institute in Paris, has made the important observation that malignant tumors in Lewis rats may produce an anti-bradykinin substance that inhibits bradykinin-induced macrophage mobility.

Because these and other vasoactive neurotransmitter substances influence lymphocyte levels of cyclic nucleotides, lymphocyte transformation by mitogens, and antigen and lymphocyte production and release of lymphokines such as interleukin 2 (IL-2), their usefulness in clinical cancer control is worthy of serious consideration.

DR. STEVEN A. ROSENBERG (Closing discussion): Studies of these tumor-infiltrating lymphocytes (TIL) reveal that they are heterogeneous. Cells that exhibit major histocompatability complex (MHC), restricted lysis, and nonrestricted lysis, are present. The demonstration that these TIL can have specific lytic reactivity against the tumor from which they are derived and not against other tumors or normal cells from that patient, probably represents the best available evidence we have today that at least some patients with cancer do mount immunologic reactions against their own established cancers.

There are several possible reasons that the TIL already present in growing tumors do not inhibit tumor growth in the original host. We give about 2 to 3 × 10^{11} lymphocytes. That is probably equivalent to the entire lymphocyte pool of the individual. These cells are grown to those large numbers in culture and part of the explanation might well be a quantitative one. The second is that there are suppressive influences that exist in the body that may affect the differentiation of these TILs that do not exist when we educate them to react against tumors outside the body.

We have recently completed a prospective randomized trial of 181 patients randomized to receive either IL-2 alone or LAK cells and IL-2. The incidence of complete responses is statistically significantly increased in those patients receiving LAK cells.

We do not now understand why some patients respond and others do not and have been unsuccessful in identifying correlates of response either in the patient or in the patient's tumor cells. We don't know the target structure that is recognized by these immune cells. We do know, however, that the lysis can be MHC restricted and that antibodies against class I histocompatibility antigens can inhibit lysis completely.

We have treated 19 patients with cyclophosphamide and IL-2 and saw two partial responses. We also treated 32 patients with monoclonal antibodies. The toxicity data, however, included all of the 652 patients. I should mention that no patient received any other form of therapy other than the immunotherapy for the 1 month before or throughout the protocol follow-up period, so all of the responses are, in fact, due to the immunotherapy and not to other concurrent treatments.

In terms of abrogating the toxicity due to IL-2 administration, we have looked at the ability of steroids to overcome many of these side effects. Unfortunately the administration of high-dose steroids also aborts the therapeutic effects of this immunotherapy.

Finally, we have not yet begun looking at other vasoactive substances administered in conjunction with IL-2, but that is probably an area worth investigating.

Serial Noninvasive Studies Do Not Herald Postoperative Failure of Femoropopliteal or Femorotibial Bypass Grafts

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We performed a 5-year retrospective case-control study of 232 patients undergoing femoropopliteal (n = 188) or femorotibial (n = 44) bypass to determine if serial noninvasive studies herald postoperative graft failure. We correlated serial ankle/arm pressure indices (API) with graft patency. An interval drop in API of ≥ 0.20 was considered hemodynamically significant, but interventional therapy was carried out only for clinically symptomatic graft failure and an API < 0.20 above the preoperative value. The cumulative 5-year limb salvage rate was 82% and the patient survival was 63%. A significant drop in API did not correlate with cumulative 5-year graft patency. The 5-year cumulative primary graft patency rates were 60% and 62% in patients with stable and interval drops in API, respectively (Z = 0.15, p = N.S.) These results suggest that a significant drop in postoperative API does not predict patients with impending femoropopliteal or femorotibial graft failure. We believe that routine noninvasive surveillance and prophylactic intervention on detected asymptomatic lesions in leg bypass grafts may not be justified.

THE MOST COMMON COMPLICATION following femoropopliteal (FP) or femorotibial (FT) bypass is graft thrombosis. The likelihood of success in restoring lasting patency to a graft that is thrombosed is much less than the secondary patency rate after intervention for a stenotic lesion that is considered a threat to graft integrity.[1] For this reason many surgeons recommend serial noninvasive surveillance of bypass grafts to permit detection of hemodynamically significant lesions amenable to interventional repair (operation or balloon dilatation) before graft thrombosis.[1-12] However many grafts fail without antecedent heralding symptoms or deterioration in hemodynamic indices.[5] Furthermore the natural history of grafts harboring hemodynamically significant lesions not subjected to prophylactic intervention is unknown. We undertook the present study to determine if serial postoperative noninvasive studies in patients undergoing infrainguinal bypass are useful in predicting patients at risk of impending graft failure.

From the Department of Surgery, University of Arkansas for Medical Sciences, and the Surgical Service, Little Rock Veterans Administration Medical Center, Little Rock, Arkansas

Methods

Study Design

We performed a retrospective, observational case-control study of all patients undergoing FP or FT bypass during a 5-year period at the University Hospital of Arkansas and the Little Rock Veterans Administration Hospital. From April 1983 through March 1988, 232 patients underwent infrainguinal bypass and had both preoperative and serial postoperative noninvasive studies available for correlation with clinical outcome of graft patency.

Patient Sample

The 232 patients included 222 men and 10 women who ranged in age from 36 to 88 years, with a mean age of 63 years. Risk factors included tobacco use in 196 patients (85%), symptomatic coronary artery disease (angina and/or previous myocardial infarction) in 105 (45%), diastolic hypertension above 90mm Hg in 104 (45%), and diabetes mellitus requiring insulin in 61 (26%). The indication for the primary bypass operation was critical limb ischemia in 160 patients (ischemic rest pain in 117 and tissue necrosis in 43) and life-style disabling claudication in 72 individuals. Infrainguinal bypass was required in

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273 limbs of the 232 patients. However, to avoid confounding outcome analysis by data from paired limbs of one individual, we restricted the reported results in this study to information from the first extremity undergoing bypass in patients with staged bilateral procedures. Results are thus available in 232 extremities.

Primary Operation

Infrainguinal bypass was performed with autogenous vein in 150 patients (65%), polytetrafluoroethylene (PTFE) in 52 (22%), and human umbilical vein or composite grafts in 30 patients (13%). Of the autogenous veins, *in situ* grafts were used in 111 patients, nonreversed translocated grafts in 23, and reversed veins in 16. The proximal anastomosis was performed at the level of the common femoral artery in 127 extremities, the superficial femoral artery in 79, the popliteal artery in 21, and to the iliac artery or limb of a previous aortofemoral prosthesis in 5 limbs. The distal anastomosis was performed at the popliteal artery in 188 extremities (81%, including above the knee in 121 and below the knee in 67) and to the infrapopliteal arteries in 44 limbs (19%).

Noninvasive Studies

All patients had preoperative and serial postoperative hemodynamic evaluation of arterial velocity waveforms with continuous-wave Doppler ultrasound, Doppler measurement of resting ankle systolic blood pressure as referenced to the arm (ankle/arm pressure index, API, normally ≥ 0.90), segmental limb blood pressure measurement, and toe pulse waveform and pressure measurements using photoplethsymography.[13] For the purpose of this study, the hemodynamic integrity of the grafted extremity was evaluated by the measurement of the resting API over time. Serial postoperative measurements of API were performed immediately after operation, before discharge from the hospital, at 1 month, and then at 3 to 6 month intervals thereafter. Because the biologic and measurement variability of API is ≤ 0.15,[14] in this study a hemodynamically significant interval change in API was considered to be ≥ 0.20. A hemodynamic graft failure was defined by an API < 0.20 above the preoperative value.

Secondary Intervention

Despite systematic postoperative surveillance with noninvasive studies, no patient underwent arteriography and prophylactic intervention for interval deterioration of API during the 5-year period of this study. Secondary operative or radiologic intervention was limited to patients with clinical and hemodynamic graft failure (API < 0.20 above preoperative value) and recurrence of symptoms.

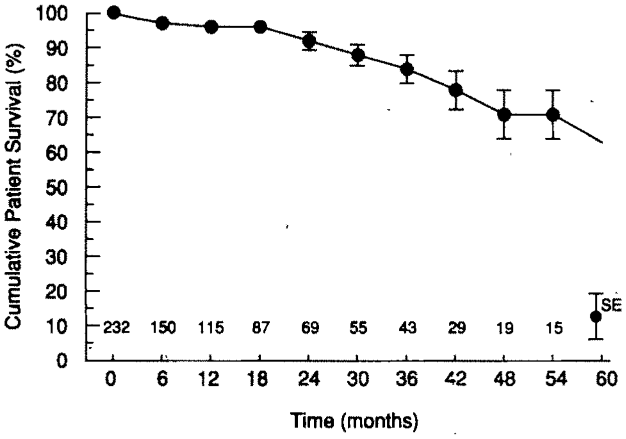

FIG. 1. Cumulative patient survival after FP or FT bypass.

Data Analysis

The primary endpoints for this study included death, amputation, and primary graft failure in the reported extremity, as documented clinically (by arteriography and/or operation) or hemodynamically (API < 0.20 above preoperative value). Cumulative patient survival, limb salvage, and primary graft patency rates were calculated by the life table method.[15] Primary graft patency was defined hemodynamically by an API ≥ 0.20 above the preoperative value in the absence of a subsequent (secondary) operative or radiologic intervention. The Fisher exact test[16] was used to test the significance of differences in overall primary graft patency rates between patients with stable postoperative API (< 0.20 decrease from the maximal postoperative value at any subsequent interval) and those patients manifesting a significant postoperative interval decrease in API (≥ 0.20). The interval difference in cumulative 5-year graft patency rates between these two groups of patients was analyzed by the Z test for a difference in proportions.[15] Values of API were expressed as group means ± one standard deviation (SD). The variance in data in cumulative life tables was expressed as standard error.

Results

Patient Survival

Twenty-one patients (9%) died during the 5-year period of this study: 2 deaths were perioperative (30 days), 2 were early postoperative (1 to 3 months), and 17 were late (3 months to 5 years). Eight patients died of myocardial infarction. No patient died of stroke. The cumulative 5-year patient survival was 63% and is depicted in Figure 1. The mean follow-up in this study was 17 ± 17 (SD) months.

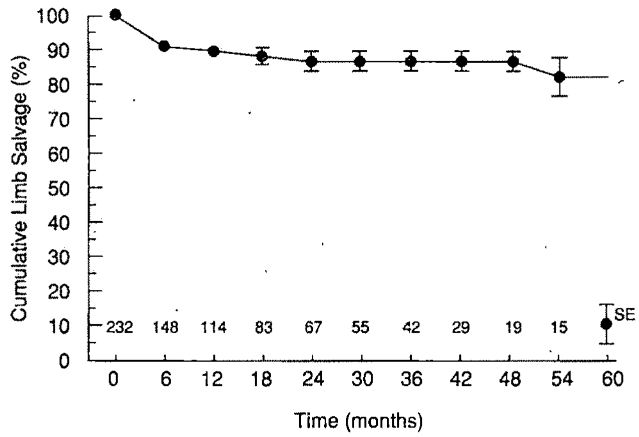

FIG. 2. Cumulative limb salvage after FP or FT bypass.

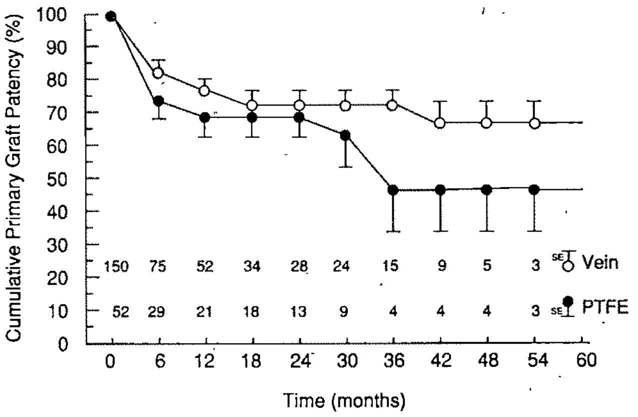

FIG. 4. Cumulative primary graft patency for autogenous vein and polytetrafluoroethylene (PTFE) following FP or FT bypass.

Limb Salvage

Amputations were performed on 24 (10%) of the reported extremities (12 in the perioperative period, 5 between 1 and 3 months, and 7 in the late postoperative period). The cumulative 5-year limb salvage rate was 82% and is depicted in Figure 2.

Graft Patency

Graft failure occurred in 62 limbs (27%), including 35 in the perioperative period, 8 between 1 and 3 months, and 19 between 3 and 42 months after operation. The cumulative 5-year primary graft patency rate was 59% and is depicted in Figure 3.

Of the 150 autogenous vein grafts, 32 (21%) failed, including 20 in the perioperative period, 4 between 1 and three months, and 8 between 3 and 42 months after operation. Of the 52 PTFE prostheses, 17 (33%) failed, including 7 in the perioperative period, 3 between 1 and 3 months, and 7 between 3 and 36 months after operation. The cumulative 5-year primary patency rates of autogenous vein and PTFE grafts were 66% and 46%, respectively, and are depicted in Figure 4 and in Tables 3, 4, and 7 in the Appendix. Although the cumulative patency rate was less for PTFE at all intervals, the test for a difference in proportions was significant (Z = 2.04) only at the 30- to 36-month interval. Of the 30 human umbilical vein or composite grafts, 11 failed (44%), including 3 in the perioperative period, 1 between 1 and 3 months, and 7 between 3 and 24 months after operation. Because of the small number of such grafts, the cumulative patency rate was not analyzed.

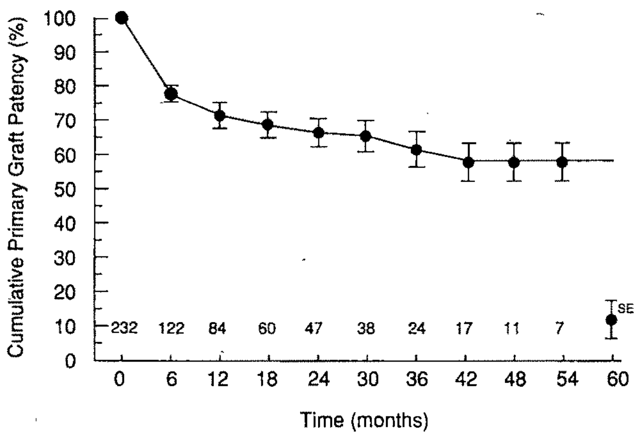

FIG. 3. Cumulative primary graft patency following FP or FT bypass.

Noninvasive Correlatives of Graft Outcome

The mean preoperative API of all patients was 0.46 ± 0.19 (SD). Of the 170 patients who maintained graft patency, the mean API rose from 0.45 ± 0.20 before operation to 0.87 ± 0.25 after operation. Of the 62 patients who developed late postoperative graft failure, the API rose from 0.51 ± 0.14 before operation to 0.90 ± 0.10 after operation. The mean API at the follow-up interval immediately preceding graft failure was 0.85 ± 0.13. These differences in mean API of patients with patent and failed grafts are not significant.

To analyze the influence of a hemodynamically significant drop in API (≥ 0.20) on graft patency during follow-up, the patients were divided into two groups. The control group consisted of 192 patients whose API remained stable throughout the postoperative period. The study (case) group consisted of the 40 patients who developed a significant drop in API of ≥ 0.20 during one or more intervals during follow-up surveillance. A comparison of the demographic characteristics of the two groups of patients is depicted in Table 1. The comparison of graft failure rates between the two groups for all patients as well as for individual graft materials is shown in Table 2. These data reveal that a significant interval drop in API did not correlate with subsequent graft failure for the entire group of patients or in any subgroup of patients based on the type of graft. The cumulative 5-year primary graft patency was 60% for patients with stable postoperative API and 62% for patients with a significant interval decline in API of ≥ 0.20. These data are illustrated in Figure 5 and in Tables 5 to 7 in the Appendix. Of interest is the fact that at 12 months the patency rate in the group of patients with a significant drop in API was significantly better than that of patients with stable postoperative API, although the curves were not significantly different for the remaining intervals of follow-up.

Discussion

The principal limitation of infrainguinal bypass is early or late graft failure. Most patients who develop recurrent symptoms or signs of limb ischemia after FP or FT bypass have developed thrombosis of the graft. However some patients harbor patent grafts with hemodynamically significant stenosis of the conduit and/or the native inflow or outflow vessels.[6] The likelihood of prolonged patency after secondary intervention for graft or host-artery stenosis is greater than for correction of a thrombosed reconstruction.[1,17-19] Indeed recent reports suggest that secondary operations for recurrent or residual stenoses have cumulative patency rates approaching those of primary vascular reconstructions.[1,12] These observations have led to the routine performance of postoperative follow-up by noninvasive studies or other objective methods to identify patients with hemodynamically significant obstruction that might jeopardize graft patency.[1-12,20,21] Such surveillance may lead to arteriography and prophylactic operation or radiologic intervention to correct lesions before graft thrombosis.[1-12,17-25]

Selective or routine postoperative arteriography remains the diagnostic standard to identify obstructive lesions affecting the bypass graft, its anastomoses, or the inflow or outflow arteries. Despite the less intrusive nature of digital angiography,[21] the expense, discomfort, and risks of arteriography preclude its use for routine postoperative surveillance of bypass grafts. Doppler ultrasound and the recent combination of ultrasonic imaging and Doppler flow analysis (duplex scanning)[10-12] have become the most widespread techniques of postoperative monitoring of patients for graft and host-vessel integrity. The measurement of resting and postexercise API is the most simple method to identify potentially flow-reducing arterial obstruction.[1-9] Previous studies have suggested that preoperative[26] or early postoperative[27] API and intraoperative blood flow[28] or outflow resistance measurements[29] correlate with early and late graft patency, but most investigations have reported that such indices do not have predictive value in identifying patients at risk for postoperative graft occlusion.[30-34] Several studies have documented that deterioration of interval API on serial follow-up correlates well with significant graft or arterial

TABLE 1. *Demographic Characteristics of Patients with Postoperative Stable and Drop (≥0.20) in Ankle/Arm Pressure Index (API)*

Patient Characteristic	Stable API (n = 192)	Drop API (n = 40)	Significance of Differences*
sex (Male)	183	39	p = 0.85
age in years (mean ± S.D.)	63 ± 8	63 ± 10	p = N.S.
tobacco use	158	38	p = 0.05
coronary artery disease	86	19	p = 0.86
hypertension	84	20	p = 0.49
Diabetes mellitus	47	14	p = 0.17
operation for critical ischemia	133	27	p = 0.85

* Using Fisher's exact probability test for significance of difference between demographic characteristics for all variables except age which was analyzed by the Student's t test.

TABLE 2. *Influence of Graft Material and Interval Ankle/Pressure Index (API) on Graft Patency*

Graft	Interval API	No. Limbs	Graft Failure	%
Vein	Stable	122	27	22
	Drop ≥ 0.20	28	5	18
	Total	150	32	21
PTFE	Stable	45	15	33
	Drop ≥ 0.20	7	2	29
	Total	52	17	33
Other	Stable	25	11	44
	Drop ≥ 0.20	5	2	40
	Total	30	13	43
Total	Stable	192	53	28
	Drop ≥ 0.20	40	9	22
	Total	232	62	27

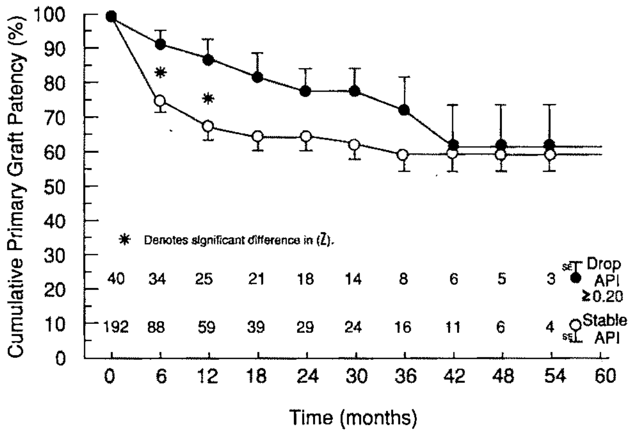

FIG. 5. Cumulative primary graft patency in patients with stable postoperative resting ankle pressure indices (API) and patients manifesting a significant drop (≥ 0.20) in API at one or more intervals after operation.

obstruction on subsequent arteriography.[1–9] More recently Bandyk et al.[10,12] and others[11] have suggested that measurements of peak systolic flow velocity and end-diastolic velocity are sensitive indicators of the hemodynamic integrity of infrainguinal bypass grafts and the host arteries. A peak systolic velocity of less than 45 cm/second has been found to correlate with early or late postoperative graft failure. Patients found to have graft peak flow velocities at or below this threshold level have undergone angiography and offending lesions have been corrected. Such prophylactic intervention has led to a subsequent cumulative graft patency rate of 81% at 4 years, which compares favorably with an 86% 4-year cumulative graft patency rate for primary reconstructions not associated with postoperative abnormalities on duplex scanning.[12]

The tendency to perform angiography and prophylactic repair of detected lesions has become particularly common since the reintroduction of *in situ* saphenous vein bypass.[35] Such interventions have been recommended both because of the frequency of retained valve cusps or arteriovenous fistulas associated with this procedure and the relative simplicity of operative repair of the subcutaneous graft. Furthermore such lesions often result in recurrent symptoms and the offending cause is readily detected both clinically and by noninvasive techniques.

Despite the common practice of routine noninvasive postoperative surveillance of patients, there is little published information about the natural history of patients who develop deterioration of API or other noninvasive parameters on serial follow-up.[1,17] Furthermore many postoperative graft occlusions occur without heralding symptoms or antecedent abnormality on the most recent follow-up noninvasive study.[5] Finally recent reports suggest that significant angiographic abnormalities may be present without coexisting abnormality of noninvasive testing.[11,12] These data suggest that the role of routine surveillance and intervention on detected lesions in bypass grafts or the native circulation remains to be established.

The present study was designed to determine if outcome of patients who developed deterioration of postoperative API was significantly worse than that of patients whose API remained stable during the follow-up period. A unique feature of this retrospective study was the policy of the senior authors (RWB and BWT) not to prophylactically intervene in patients with postoperative abnormality on noninvasive study unless clinically significant manifestations of limb ischemia had recurred. Thus no patient had surgical or radiologic intervention before graft failure during the 5-year period of this study. A second feature of this study was the use of a consistent protocol of follow-up of all patients in the noninvasive vascular laboratory to define the natural history of arterial reconstruction. Third the hemodynamic index of graft and native arterial integrity was the resting API. This test, while not necessarily as sensitive to graft or arterial obstruction as duplex scanning and Doppler spectral analysis, is widely used, simple, and reproducible.[14] Furthermore to identify patients who harbor significant graft or arterial obstruction, the resting API is the most appropriate test to evaluate the rationale of prophylactic intervention on detectable lesions before graft thrombosis. If the presence of major arterial obstruction sufficient to cause a significant reduction in resting API does not correlate with adverse graft outcome, then detection of less severe lesions with a more sensitive test would appear to be inappropriate.

We established the criterion of a hemodynamically significant change in interval API (≥ 0.20) before the retrospective review. This figure is based on the reported biologic and measurement variance in measurement of resting API (≤ 0.15)[14] and is also the criterion used by several investigators, including an ongoing multicenter trial of bypass grafts that is supported by the Veterans Administration. We likewise established the criterion of hemodynamic graft failure (< 0.20 above the preoperative value) before reviewing the patient records. Finally the allocation of patients into the two groups with and without stable postoperative interval resting API was a stated objective at the start of this review. Such steps were necessary to avoid the bias inherent in *post hoc* analyses, particularly in retrospective studies.[36]

Our study revealed that deterioration of resting API (≥ 0.20) during longitudinal follow-up does not herald impending graft failure in patients undergoing FP or FT bypasses. This lack of correlation between a decrease in interval API and adverse graft outcome was true not only for autogenous vein grafts but also for other materials, including PTFE and human umbilical vein used in this study. Although the cumulative patency rate for PTFE was worse than that for autogenous saphenous vein grafts (significant only at 36 months), the within-group cumulative patency rates for a given conduit were not significantly different for patients with stable postoperative API and those with a significant deterioration in interval API.

There are several limitations to the present study that may affect its general value. First it is retrospective in design and thus subject to the drawbacks of such studies.[36] Second we limited the noninvasive surveillance to resting pressure measurements and did not use hyperemia testing or Doppler (or duplex) flow analysis, which are recognized to be more sensitive indices of arterial abnormality.[10,12,13] Third we did not perform angiographic confirmation of the presence and location (graft, inflow, and outflow vessel) of arterial obstruction in patients with an abnormal interval resting API. Fourth the number of patients with different types of grafts was unequal, representing our preferences for the materials used. Fifth our study reports outcomes of patients from two different hospitals (Veterans and University) and two surgeons. Sixth despite a total follow-up period of 5 years, the mean follow-up was only 17 ± 17 months (± 1 SD). Finally the sample size of this study may be insufficient to exclude a type II error or false-negative study.[36] A posterior β analysis with a sample of 232 patients suggests a power of only 10% for the observed 5% difference between the outcome of the patients with and without a significant drop in API. This sample size would have a power of 80% (β of 0.20) in detecting only a 20% difference in graft patency rate between the two groups.

Despite these limitations, we believe these observations are important and deserve future study. As mentioned before, we approached this retrospective study in a manner to reduce the bias of *post hoc* analysis. Furthermore we believe the data reflect a value of a retrospective study, namely to generate a hypothesis that will require further prospective study.[36] Such an investigation is planned, recognizing that to achieve statistical significance a multicenter trial may be necessary. The rationale for use of serial resting API measurements after operation, which are potentially insensitive,[21] has been previously mentioned. In a planned prospective study, the relative roles of API and Doppler or duplex flow analysis[12] should be investigated. The absence of angiographic confirmation of the presence and location of detected postoperative arterial obstruction might be addressed in a prospective study. However the increasing use of duplex scanning for both vessel imaging and flow analysis may be a sensitive and less intrusive alternative in future investigations.[10,12] Such studies should endeavor to follow patients with different grafts in sufficient numbers to clearly define the natural history of detected obstruction or the efficacy of prophylactic intervention on such lesions. Any future trial should attempt to minimize differences in patient samples or surgical technique, which remain substantive reasons for differences in reported outcome of infrainguinal bypass. Finally future studies should involve a sufficient sample size and extend for a sufficient period of follow-up to clearly define the long-term risk of graft failure in patients with or without detectable vascular defects.

Two concerns remain in designing a future study to investigate the roles of postoperative noninvasive monitoring and prophylactic intervention on residual/recurrent arterial obstruction after infrainguinal bypass. The first relates to the propriety in obtaining angiographic documentation of lesions detected by noninvasive screening. While duplex scanning offers sensitive flow and imaging information, especially in superficial *in situ* grafts, angiography would be advisable for establishing the character of lesions, particularly in subfascial grafts or for disease of inflow and outflow vessels.[2] The second concern relates to the relative value of an observational (cohort) study of the natural history of detected lesions *versus* a randomized trial comparing prophylactic intervention with observation of such lesions. While the latter design might be preferable, a larger patient sample size and thus a multicenter trial would be necessary.[36]

This retrospective study suggests that routine postoperative surveillance by noninvasive measurement of resting API in patients undergoing infrainguinal bypass may have a more limited role than previously considered. Our review suggests that patients who develop a significant drop in resting API (≥ 0.20) at one or more intervals after operation are at no greater risk of graft failure than patients who have a stable API during serial follow-up. This finding is true not only for patients with autogenous vein grafts but also with PTFE and human umbilical vein or composite grafts. The implication of this study is that the ability to reliably identify the patient whose graft will fail without secondary intervention is yet to be perfected. Perhaps such detectable lesions after infrainguinal bypass have a natural history somewhat akin to that of carotid lesions. If so, as with carotid disease, a prospective randomized trial may be necessary to justify the routine noninvasive detection and prophylactic repair of lesions after arterial bypass of the lower extremity.

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Appendix

TABLE 3. *Life Table Analysis of Primary Graft Patency for Autogenous Vein Following Femoropopliteal or Femorotibial Bypass*

Months of Observation	O_x	d_x	w_x	q_x	p_x	P_x	$SE(P_x)$
0–1	150	20	27	0.15	0.85	0.85	0.030
>1–3	103	4	11	0.04	0.96	0.82	0.034
>3–6	88	0	13	0.00	1.00	0.82	0.034
>6–12	75	5	18	0.08	0.92	0.76	0.041
>12–18	52	2	16	0.05	0.95	0.72	0.046
>18–24	34	0	6	0.00	1.00	0.72	0.046
>24–30	28	0	4	0.00	1.00	0.72	0.046
>30–36	24	0	9	0.00	1.00	0.72	0.046
>36–42	15	1	5	0.08	0.92	0.66	0.070
>42–48	9	0	4	0.00	1.00	0.66	0.070
>48–54	5	0	2	0.00	1.00	0.66	0.070
>54–60	3	0	3	0.00	1.00	0.66	0.070

O_x, Success and under observation at the beginning of interval; d_x, failure during interval; w_x, withdrawn a success during the interval; q_x, chance of failure in interval; p_x, chance of success in interval; P_x, cumulative chance of success; $SE(P_x)$, standard error of the cumulative chance of success (where the terms success or failure are used to classify the desirable or undesirable result).

TABLE 4. *Life Table Analysis of Primary Graft Patency for Polytetrafluroethylene (PTFE) Following Femoropopliteal Bypass*

Months of Observation	O_x	d_x	w_x	q_x	p_x	P_x	$SE(P_x)$
0–1	52	7	6	0.14	0.86	0.86	0.050
>1–3	39	3	0	0.08	0.92	0.79	0.059
>3–6	36	2	5	0.06	0.94	0.74	0.064
>6–12	29	2	6	0.08	0.92	0.69	0.071
>12–18	21	0	3	0.00	1.00	0.69	0.071
>18–24	18	0	5	0.00	1.00	0.69	0.071
>24–30	13	1	3	0.09	0.91	0.63	0.086
>30–36	9	2	3	0.27	0.73	0.46	0.119
>36–42	4	0	0	0.00	1.00	0.46	0.119
>42–48	4	0	0	0.00	1.00	0.46	0.119
>48–54	4	0	1	0.00	1.00	0.46	0.199
>54–60	3	0	3	0.00	1.00	0.46	0.119

O_x, Success and under observation at the beginning of interval; d_x, failure during interval; w_x, withdrawn a success during the interval; q_x, chance of failure in interval; p_x, chance of success in interval; P_x, cumulative chance of success; $SE(P_x)$, standard error of the cumulative chance of success (where the terms success or failure are used to classify the desirable or undesirable result).

TABLE 5. *Life Table Analysis of Patients Manifesting a Significant Drop (≥0.2) in API at One or More Intervals After Operation*

Months of Observation	O_x	d_x	w_x	q_x	p_x	P_x	$SE(P_x)$
0–1	40	2	2	0.05	0.95	0.95	0.04
>1–3	36	0	0	0.00	1.00	0.95	0.04
>3–6	36	1	1	0.03	0.97	0.92	0.04
>6–12	34	2	7	0.07	0.93	0.86	0.06
>12–18	25	1	3	0.04	0.96	0.82	0.07
>18–24	21	1	2	0.05	0.95	0.78	0.07
>24–30	18	0	4	0.00	1.00	0.78	0.07
>30–36	14	1	5	0.09	0.91	0.72	0.09
>36–42	8	1	1	0.13	0.87	0.62	0.12
>42–48	6	0	1	0.00	1.00	0.62	0.12
>48–54	5	0	2	0.00	1.00	0.62	0.12
>54–60	3	0	3	0.00	1.00	0.62	0.12

O_x, Success and under observation at the beginning of interval; d_x, failure during interval; w_x, withdrawn a success during the interval; q_x, chance of failure in interval; p_x, chance of success in interval; P_x, cumulative chance of success; $SE(P_x)$, standard error of the cumulative chance of success (where the terms success or failure are used to classify the desirable or undesirable result).

TABLE 6. *Life Table Analysis of Patients with Stable Postoperative Resting Ankle Pressure Indices (API)*

Months of Observation	O_x	d_x	w_x	q_x	p_x	P_x	$SE(P_x)$
0–1	192	33	33	0.19	0.81	0.81	0.03
>1–3	126	8	11	0.07	0.93	0.76	0.03
>3–6	107	1	18	0.01	0.99	0.75	0.03
>6–12	88	7	22	0.09	0.91	0.68	0.04
>12–18	59	2	18	0.04	0.96	0.65	0.04
>18–24	39	0	10	0.00	1.00	0.65	0.04
>24–30	29	1	4	0.04	0.96	0.63	0.05
>30–36	24	1	7	0.05	0.95	0.60	0.05
>36–42	16	0	5	0.00	1.00	0.60	0.05
>42–48	11	0	5	0.00	1.00	0.60	0.05
>48–54	6	0	2	0.00	1.00	0.60	0.05
>54–60	4	0	4	0.00	1.00	0.60	0.05

O_x, Success and under observation at the beginning of interval; d_x, failure during interval; w_x, withdrawn a success during the interval; q_x, chance of failure in interval; p_x, chance of success in interval; P_x, cumulative chance of success; $SE(P_x)$, standard error of the cumulative chance of success (where the terms success or failure are used to classify the desirable or undesirable result).

TABLE 7. *The Z Statistic for a Difference in Sample Proportions Was Used to Compare Each Interval (Months of Observations) of the Life Table Analyses Shown as Figures 4 and 5*

	Figure 4			Figure 5		
	Cumulative Probability of a Success for the Interval		Z	Cumulative Probability of a Success for the Interval		Z
Months of Observation	^{P}Vein	^{P}PTFE	(^{P}Vein-^{P}PTFE)	^{P}Stable	^{P}Drop	(^{P}Stable-^{P}Drop)
0–1	0.85	0.86	0.17	0.81	0.95	2.80*
>1–3	0.82	0.79	0.44	0.76	0.95	3.80*
>3–6	0.82	0.74	1.10	0.75	0.92	3.40*
>6–12	0.76	0.69	0.85	0.68	0.86	2.43*
>12–18	0.72	0.69	0.36	0.65	0.82	2.10*
>18–24	0.72	0.69	0.36	0.65	0.78	1.60
>24–30	0.72	0.63	0.92	0.63	0.78	1.74
>30–36	0.72	0.46	2.04*	0.60	0.72	1.17
>36–42	0.66	0.46	1.45	0.60	0.62	0.15
>42–48	0.66	0.46	1.45	0.60	0.62	0.15
>48–54	0.66	0.46	1.45	0.60	0.62	0.15
>54–60	0.66	0.46	1.45	0.60	0.62	0.15

* Denotes a significant difference in sample proportions at the time interval. The difference in sample proportions is significant if the calculated Z meets or exceeds $Z_{\alpha.05} = 1.96$, where $Z = {}^P\text{success} - {}^P\text{failure}/\sqrt{[SE\,({}^P\text{success})]^2 + [SE\,({}^P\text{failure})]^2}$.

DISCUSSION

DR. JONATHAN TOWNE (Milwaukee, Wisconsin): We agree that postoperative surveillance is unable to reliably detect impending graft failure in PTFE conduits. We also agree that ankle brachial indices alone are not a sensitive enough test for postoperative surveillance. Approximately 50% of our patients are diabetics, of whom at least one third have incompressible vessels that make measurements of ankle brachial indices impossible. Therefore, at the suggestion of Dennis Bandyk, my colleague, 6 years ago, we have added the measurement of graft flow velocity to our surveillance protocol, which has markedly increased the sensitivity for detecting the failing but patent bypass graft.

We disagree with the value of postoperative surveillance to detect a failing vein bypass graft. In a prospective surveillance protocol involving 250 distal grafts followed at three monthly intervals with both ankle brachial indices and graft flow velocity, we have detected problems requiring revision in 20% of grafts, most occurring less than 24 months after operation.

There are several factors that may explain the disparity of our data with the authors. Eighty-one per cent of the authors' grafts were to the popliteal artery, almost two thirds of which were to the above-knee popliteal. In our series, three fourths were to the tibial vessels. The longer graft in our series has a greater chance of developing fibrointimal hyperplasia at valve incision sites. Fibrointimal hyperplasia at the distal anastomosis of a 1- to 2-millimeter tibial vessel will cause significant flow reduction sooner than at the larger popliteal artery. The incidence of claudication as an indication for operation was 30% in the authors' series compared to 5% in our series, indicating that the groups have slightly different levels of atherosclerotic occlusive disease. Finally the authors' surveillance protocol was 3 to 6 months. We believe that 6 months is too long a follow-up interval because a stenosis occasionally occurs and rapidly progresses to occlusion within a 6-month interval.

I would like to ask Dr. Barnes what portion of his grafts were at a greater than 3 months' surveillance interval. I would also like to ask him what was the incidence of incompressible vessels secondary to diabetes mellitus. We believe that the vein graft has a dynamic biology and future attempts to increase long-term patency will come from careful postoperative surveillance with identification of the failing but patent graft before thrombosis.

DR. ROBERT P. LEATHER (Albany, New York): My comments are very analogous to those of Jon Towne. I agree with the authors that the ankle brachial index is inadequate. Furthermore the interval of observation is too long because we have found that it is necessary to see these patients in the first year at 3-month intervals to pick up bypass-threatening lesions before they go on to occlusion.

We have had a prospective surveillance program in place for more than 10 years. Four years ago we added duplex ultrasound, which has now covered 285 bypasses with vein to the tibial level, with a minimum follow-up period of 1 year and many extending to 3 years. If you remember back 20 or so years ago, it was common practice to measure the volume flow in response to reactive hyperemia by the intra-arterial installation of papavarine, and if it was less than 50% the prognosis was poor. If the reactive hyperemia induced by occlusion for three minutes by pneumatic cuff did not respond with a twofold increase, this was correlated highly in identifying the failing graft.

The bottom line in our estimation is that identifying these lesions has increased the secondary patency, as I showed last year, a minimum of 15% in bypass patency but 5 years by life table analysis.

DR. DAVID S. SUMNER (Springfield, Illinois): I find myself in the rather awkward position of having to support Dr. Barnes' somewhat iconoclastic position on this issue. Like Dr. Barnes, my policy has been to follow patients who have had infrainguinal bypasses with serial ankle pressure determinations. Yet, in a review of 285 patients undergoing such operations, I identified only 15 (5%) in whom drops in ankle pressure provided the impetus to revise bypass grafts before failure. Of 30 limbs with failed grafts, only 8 (27%) dropped their ankle index by more than 20 points before occlusion; and the average prefailure index was 0.97 ± 0.17. Twenty-three (77%) had normal ankle indices greater than 0.90. Two thirds of these patients had been studied within 3 months of their graft failure.

Because ankle pressures are recognized to be an accurate method for assessing the adequacy of the peripheral circulation and should, therefore, reflect the function of a bypass graft, how do we explain these results? Several explanations come to mind. (1) Pressures will not ordinarily fall perceptibly until the graft diameter is reduced by 50% or more. (2) Pressures usually drop precipitously rather than gradually, both because of hemodynamic principles and because the final event is often sudden thrombosis. Thus the studies may not be done in close enough proximity to the final event. (3) Pressures measured with the cuff placed over a distal bypass graft extending to the ankle region will not be accurate. Because flow ceases while the cuff is inflated, measurements are made on a static column of blood and reflect the pressure at the origin of the graft—in the common femoral artery, for example. Even if a significant narrowing were present, it would not be detected.

Although serial ankle pressure measurements may not serve to alert the surgeon to impending graft failure, I believe it is too early to "throw the baby out with the bath water." Ankle pressures help assess the results of arterial reconstruction, help document the longevity of graft function, and help characterize the natural history of arterial obstructive disease. For detecting lesions developing in grafts that may lead to their early failure, surveys with duplex ultrasound appear to hold the most promise. In our recent experience using the color-flow imager in the follow-up of 37 femorotibial grafts, we identified 21 AV fistulas that were not recognized at the time of operation and 14 stenoses that developed subsequently, two of which were symptomatic and have been operated on.

I would like to ask Dr. Barnes what the average time interval was between the last ankle pressure determination and graft failure and does he think that this played a role in his findings. Also where does he feels we should go from here? Should we dispense with ankle pressure measurements and rely totally on duplex scanning? Would this approach be cost-effective?

DR. JOHN A. MANNICK (Boston, Massachusetts): Bob I think that in your manuscript you suggest that you did, in fact, reoperate on some of these patients who had greater drops in ankle pressure and also recurrent symptoms. How many of those cases actually were in the series, and does not that fact somewhat confound the conclusion you have drawn because if you really have reoperated on patients with big drops in pressure while the graft was still patent, isn't this an argument in favor of getting these measurements?

DR. ROBERT W. BARNES (Closing discussion): Dr. Towne, I recognize that in some diabetic patients incompressible vessels preclude accurate measurement of ankle pressure. We did not include such patients in our study because follow-up ankle pressure indices would not accurately reflect changes in the hemodynamic status of the bypass grafts or the host vessels. This may explain our somewhat lower prevalence of diabetes in our study compared to yours.

Your publication with Dennis Bandyk using duplex scanning for follow-up of *in situ* bypass vein grafts documents the value of this technology in detecting early lesions in these patients.

Our concern from our retrospective review, however, is that if lesions that are associated with a significant drop in ankle pressure do not herald impending graft failure, why should earlier lesions be searched for and subjected to intervention? Obviously only a prospective study will answer that question.

You asked about the mean follow-up interval between the last noninvasive study before graft thrombosis. All patients had been seen within a 6-month period before graft failure, although we did not calculate the mean interval between the last laboratory visit and the graft occlusion.

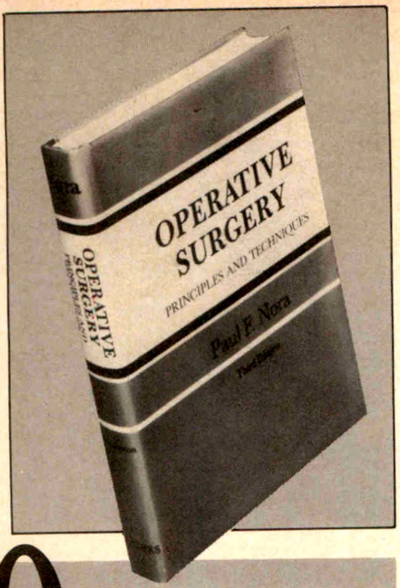
Dr. Leather I obviously appreciate your experience in prospectively surveying these grafts. In fact I believe that it is the reintroduction of the use of *in situ* vein grafting that has led to a lot of our postoperative surveillance, particularly to pick up lesions that may be corrected easily with the grafts in the subcutaneous position. I respect your rather sensitive indicator of failure of flow in the graft to increase at least twice the resting level after a period of reactive hyperemia. That certainly would be an even more sensitive indicator of early graft problems. Whether all such lesions should be intervened on remains in question.

It bothers me to place Dr. Sumner in an awkward position, but I consider him to be one of the world's best vascular physiologists. I appreciate that on short notice he reviewed some of his own data, which supports our own hypothesis.

Your first question was addressed in my answer to Dr. Towne regarding the mean interval between the last laboratory visit and graft failure, which was within 6 months in our study.

Where should we go from here? As I mentioned, retrospective studies do not prove hypotheses. They only generate hypotheses and are fairly sensitive in doing so. However a prospective study is necessary to settle this question and will undoubtedly require a multicenter trial.

Dr. Mannick, I thank you for your comments. Our reoperations, although occasionally for stenotic but patent grafts, were mostly performed in symptomatic patients who had functional hemodynamic graft failure. As your group has reported, as have researchers from Northwestern, some of these patients may still have patent grafts at the time we operate on them for functionally failed grafts. However the majority harbor occluded grafts. Nevertheless our inability to show that the failure rate is greater in patients who manifest drops in ankle pressure suggests that we must initiate a multicenter randomized trial to resolve this dilemma.



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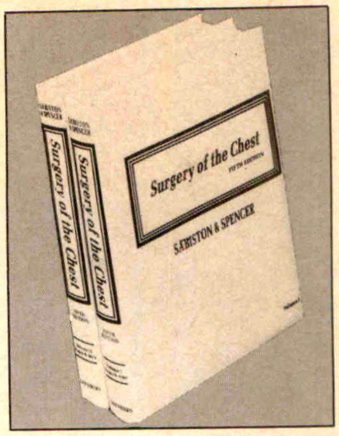

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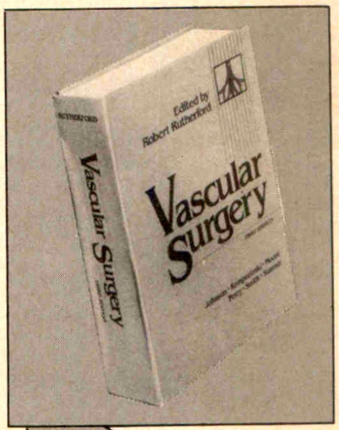

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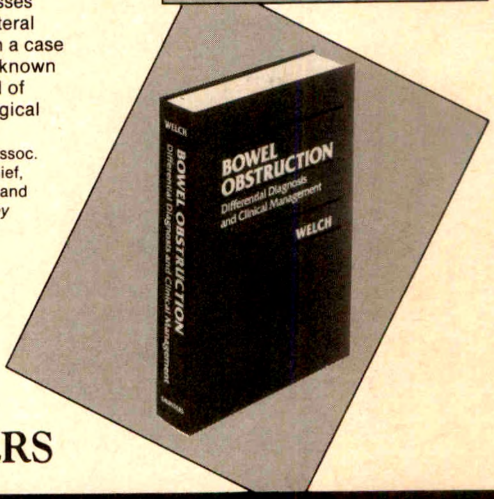

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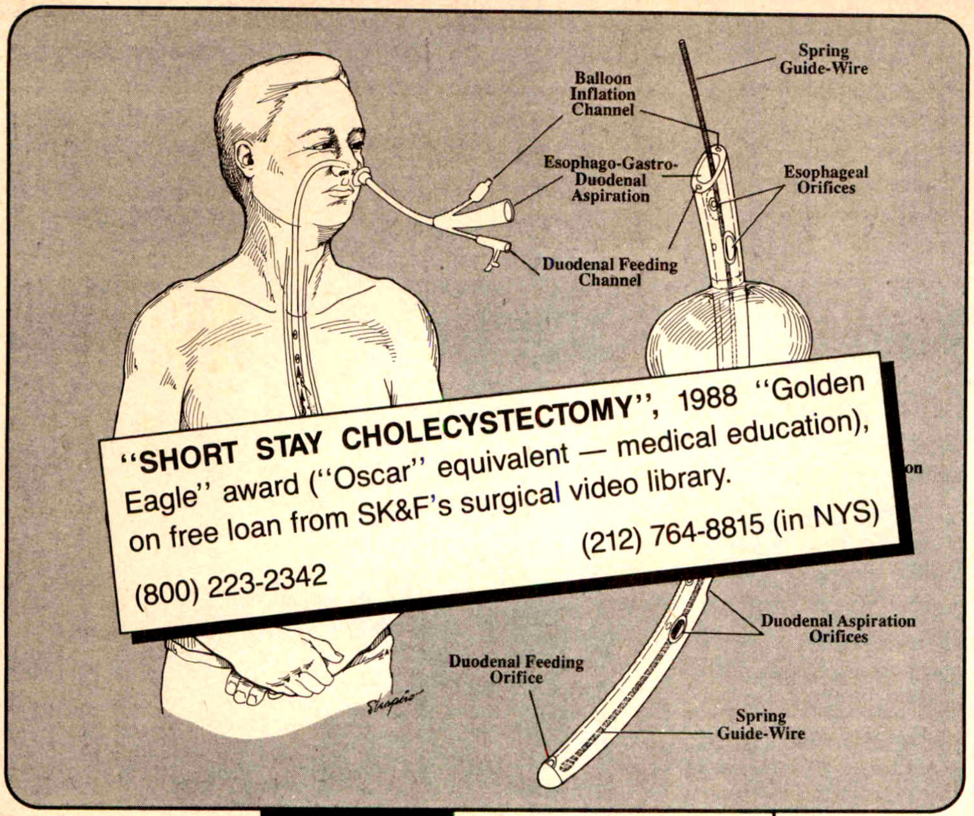

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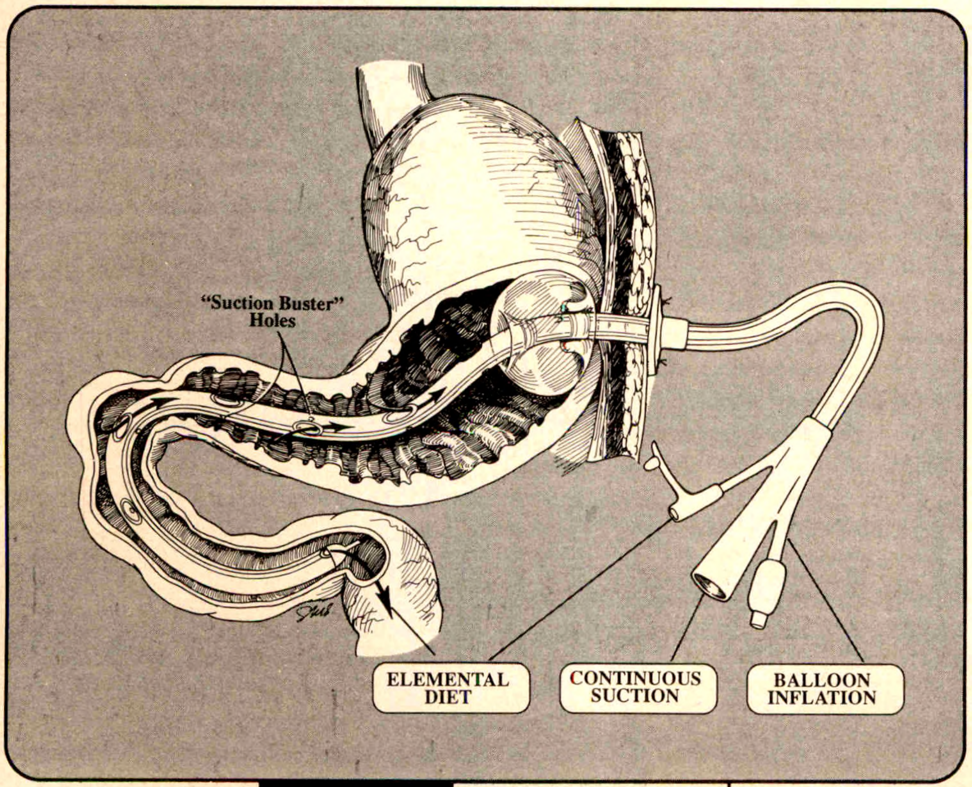

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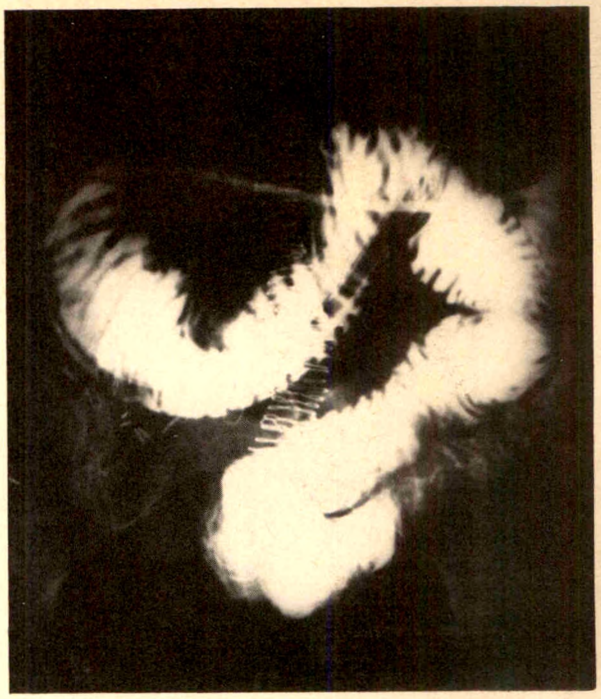
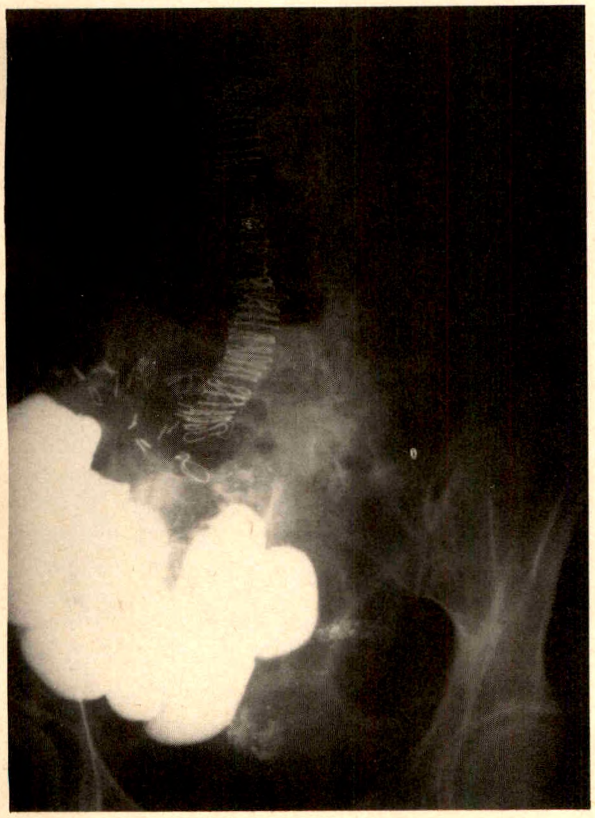
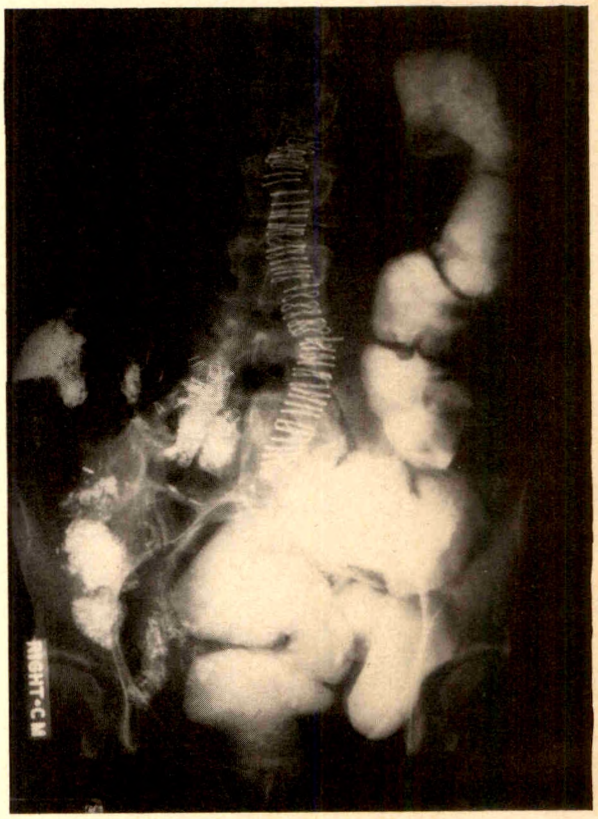


A. Study @ 5 minutes (5 hours postop).
Note efficient removal of all excess barium, with none reaching the stomach.



B. Motility @ 4 hours (9 hours postop).
All barium is within the ileum.



C. Motility @ 16 hours (21 hours postop).
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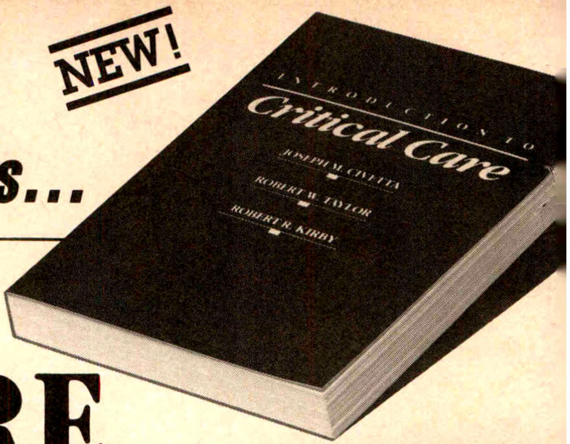

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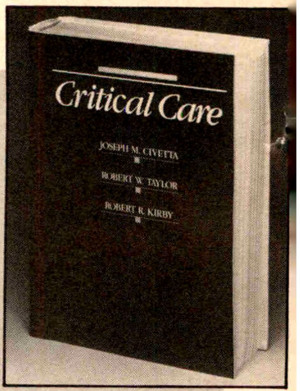

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Prediction of Pancreatic Necrosis by Dynamic Pancreatography

EDWARD L. BRADLEY III, M.D.,* FREDERICK MURPHY, M.D., and CHARLES FERGUSON, M.D.*

From the Departments of Surgery and Radiology,*
Emory University School of Medicine and
Affiliated Hospitals, Atlanta, Georgia

Parenchymal necrosis has recently been recognized as the principal determinant of the incidence of secondary infection in acute pancreatitis. Because secondary infection of pancreatic necrosis accounts for more than 80% of all deaths from acute pancreatitis, a method for determining the presence or absence of parenchymal necrosis would offer considerable prognostic and therapeutic information. Thirty seven patients with unequivocal acute pancreatitis and five normal controls were prospectively studied with intravenous bolus, contrast-enhanced computed tomography (dynamic pancreatography). In the absence of pancreatic necrosis, there were no significant differences in parenchymal enhancement between any of the following patient groups: controls (5), uncomplicated pancreatitis (20), pancreatic abscess (7), or peripancreatic necrosis (4) ($p < 0.05$). On the other hand, pancreatic parenchymal enhancement was significantly reduced or absent in all six patients with segmental or diffuse pancreatic necrosis ($p < 0.05$). Postcontrast pancreatic parenchymal enhancement was also found to be inversely correlated with the number of Ranson signs ($p < 0.001$). Dynamic pancreatography offers prognostic information and is a safe and reliable technique for predicting the presence or absence of pancreatic parenchymal necrosis.

DESPITE SIGNIFICANT ADVANCES in supportive and resuscitative care, the overall mortality rate from acute pancreatitis has remained remarkably constant at 10% to 12% for the past 40 years.[1,2] Today few patients succumb from the consequences of hypovolemia in the early phase of acute pancreatitis. Rather 80% of current deaths from acute pancreatitis can be attributed to infectious complications that occur later in the course of the disease.[3,4]

For some time it has been recognized that the incidence of infectious complications in acute pancreatitis was directly related to the clinical severity of the attack.[5] More recently, however, a link has been established between the severity of clinical presentation and pancreatic histology; in particular, the presence or absence of pancreatic necrosis.[6,7] Because of these observations, increasing attention has been paid to pancreatic parenchymal necrosis, not only as a principal determinant of the severity of an episode of acute pancreatitis, but also as a primary risk factor for pancreatic infection.[8]

Due to the pivotal role that the development of pancreatic necrosis plays with regard to clinical decision making in patients with severe acute pancreatitis, considerable efforts are being made to find a safe, reliable, and minimally invasive technique for detecting the presence of parenchymal necrosis. The present report describes our experiences with a noninvasive technique for measuring the integrity of the pancreatic microcirculation by parenchymal contrast enhancement, using commonly available equipment and materials.

Patients and Methods

Pancreatic parenchymal enhancement was prospectively studied in thirty seven patients with unequivocal acute pancreatitis. The diagnosis of acute pancreatitis was established in each patient by a combination of typical pain patterns, abdominal tenderness or guarding, leukocytosis, an elevated serum amylase or lipase, and a noncontrast CT scan demonstrating either swelling of the gland or extrapancreatic extensions of inflammation. A number of other patients, originally diagnosed as having probable acute pancreatitis, were excluded from further study by these stringent criteria. In this group of 37 patients, there were 21 male and 16 female patients with an average age of 41.3 years. The underlying pancreatitis was

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Presented at the 109th Annual Meeting of the American Surgical Association, Colorado Springs, Colorado, April 10–12, 1989.

Correspondence and reprint requests to: E.L. Bradley III, M.D., Department of Surgery, 1968 Peachtree Road, Atlanta, GA 30309.

Accepted for publication: April 17, 1989.

TABLE 1. *Average Aortic and Pancreatic Parenchymal Densities (Hounsfield Units)*

Patient Groups	# Pts.	Ranson Signs	Before Intravenous Contrast				After Intravenous Contrast		
			Aorta	Head	Body	Tail	Aorta	Pancreas	Pancreas:Aorta*
Controls	5	N/A	49	50	48	42	131	92	70%
I Uncomplicated pancreatitis	20	1.1	42	41	39	36	137	88	64%
II Pancreatic abscess	7	3.6	41	42	41	37	126	71	56%
III Peripancreatic necrosis	4	5.5	39	47	41	40	123	79	64%
IV Pancreatic necrosis (<50%)	2	4.0	36	37	33	29	118	54	46%†
V Pancreatic necrosis (>50%)	4	6.0	38	40	36	34	139	28‡	20%‡
Total (Avg)	42		(41)	(43)	(40)	(36)	(129)		

* Significant inverse correlation with number of Ranson signs ($p < 0.001$).

† Significantly different from controls ($p < 0.05$).

‡ Significantly different from all other groups ($p < 0.05$).

judged to be due to alcohol in 18, gallstones in 14, hyperlipidemia in 2, and drug reaction in 1. The pancreatitis was idiopathic in two cases. Five patients (three male, two female, average age 45.2 years), without known pancreatic disease, and who were undergoing computed tomography for other purposes, served as controls.

After giving informed consent, each of the 42 patients underwent dynamic pancreatography using either the Picker 1200 (Cleveland, OH) or the General Electric 9800 (Milwaukee, WI) computed tomographic scanners. Dynamic pancreatograms were initially performed within 48 hours of admission and were repeated as clinically indicated. Each study was preceded by routine CT scanning of the abdomen, using oral contrast and 10 mm sections to locate the pancreas in a cranial-caudal plane. Preliminary scanning also served to demonstrate any extrapancreatic collections or extensions of the inflammatory process, and to eliminate the presence of other intra-abdominal pathologic conditions. When possible precontrast density (Hounsfield units) was measured in each segment of the pancreas.

Two methods of intravenous contrast administration were studied. In the first 100 cc of iothalamate meglumine 60% was injected by pressure injector for 5 seconds, using two intravenous lines. Scanning was begun simultaneously with the onset of injection. In the second, 150 cc of contrast (200 cc for weight > 150 lbs) was given by pressure/injector at the rate of 2 to 5 cc/sec. Scanning was initiated 20 seconds after beginning the injection.

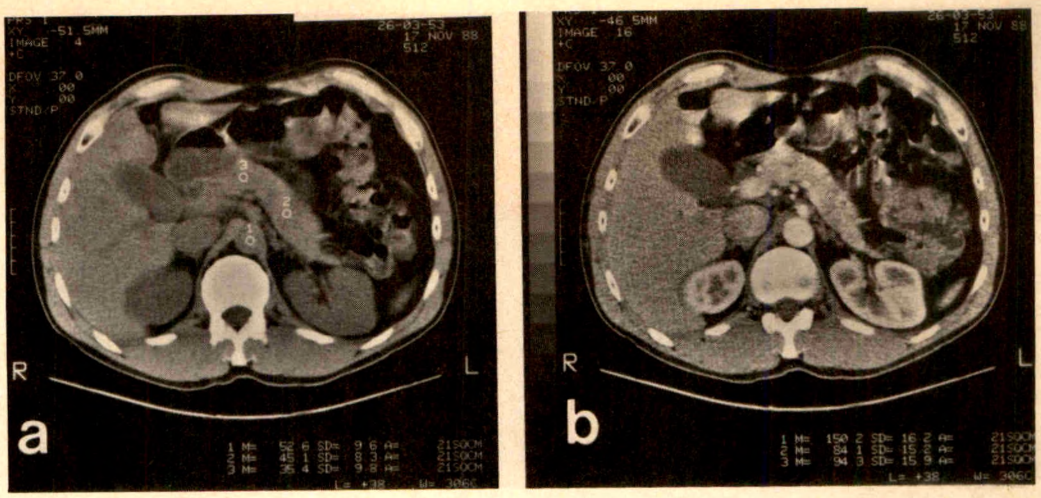
During the dynamic phase, scanning was restricted to the previously localized pancreas, using 5 mm sections at 5 mm intervals. Contrast density (Housefield units) was measured in three areas of the pancreas in each of the multiple tomographic sections, care being taken to avoid the contrast-filled splenic, superior mesenteric, and portal veins. Simultaneous contrast measurements were taken from the aorta in each tomogram to serve as a density reference for pancreatic tissue. Densities of any extrapancreatic collections or extensions of the pancreatic process were also noted.

Prospective predictions of the presence of pancreatic necrosis were based on whether the pancreatic parenchyma failed to be enhanced with dynamic pancreatography. Measurements of the presence or absence of pancreatic enhancement were compared to the individual hospital course. Patients were grouped into controls or one of five other clinical disease classifications (I Uncomplicated Acute Pancreatitis, II Pancreatic Abscess, III Peripancreatic Necrosis, IV Pancreatic Necrosis < 50%, and V Pancreatic Necrosis > 50%), using a combination of previously described clinicopathologic definitions[9] and the subsequent hospital course of each individual. Histomorphologic confirmation of the clinicopathologic classification was obtained in sixteen of the seventeen complicated cases.

In an effort to minimize differences between patients due to body geometry, plasma contrast concentration, cardiac output, or blood volume, pancreatic tissue density measurements after intravenous contrast administration were referenced to intra-aortic density by means of a pancreas: aorta ratio, thereby creating a form of internal control for each individual. The effect of time on postcontrast density measurements was minimized by averaging density values for the aorta and the pancreas in each patient. Data analysis was carried out by one way analysis of variance using Tukey's Multiple Pairwise test, and the Pearson Correlation Coefficient.

Results

The results of time–density measurements from dynamic pancreatography are shown in Table 1. In general, there was a tendency for precontrast density to fall with progression from the head of the pancreas to the tail, the average density decreasing from 43 HU in the head to 36



FIGS. 1A and B. Dynamic pancreatogram in a control patient. (A) Precontrast density is 52.6 HU in the aorta (1M), 45.1 HU in the tail of the pancreas (2M), and 35.4 HU in the body of the pancreas (3M). (B) During the dynamic phase, note the rise in corresponding aortic and pancreatic densities and the overall enhancement of the pancreatic parenchyma. (pancreas:aorta ratio, 60%)

HU in the tail. There were no significant differences in precontrast pancreatic parenchymal density between any of the patient groups ($p > 0.05$), reinforcing previous observations that routine computed tomography cannot differentiate parenchymal necrosis from pancreatic edema.

When intravenous contrast was given, there was an approximate threefold increase in aortic density, whereas only a twofold increase occurred in average pancreatic density. In the five control patients (group I), pancreatic parenchymal enhancement was prompt, equally distributed in all segments of the gland, and averaged 70% of aortic density (Fig. 1). In the absence of pancreatic necrosis (controls, groups I to III), there were no significant differences noted in either the average pancreatic parenchymal contrast density, or in segmental contrast density of the head, body or tail of the pancreas ($p > 0.05$) (Fig. 2). Postcontrast pancreatic parenchymal density was greater than 50 HU in controls, and in each case of uncomplicated acute pancreatitis (Fig. 3), pancreatic abscess (Fig. 4), and peripancreatic necrosis (Fig. 5). No patient with parenchymal enhancement > 50 HU was subsequently proved to have pancreatic necrosis.

On the other hand, significant reductions in average and segmental parenchymal enhancement ($p < 0.05$) and in the pancreas:aorta density ratio ($p < 0.05$) occurred in all six patients with subsequently proved pancreatic necrosis (groups IV and V; positive predictive value 100%). In each of the patients with segmental or diffuse pancreatic necrosis, parenchymal density in the involved segment(s) was less than 40 HU (Figs. 6 and 7). Perhaps more im-

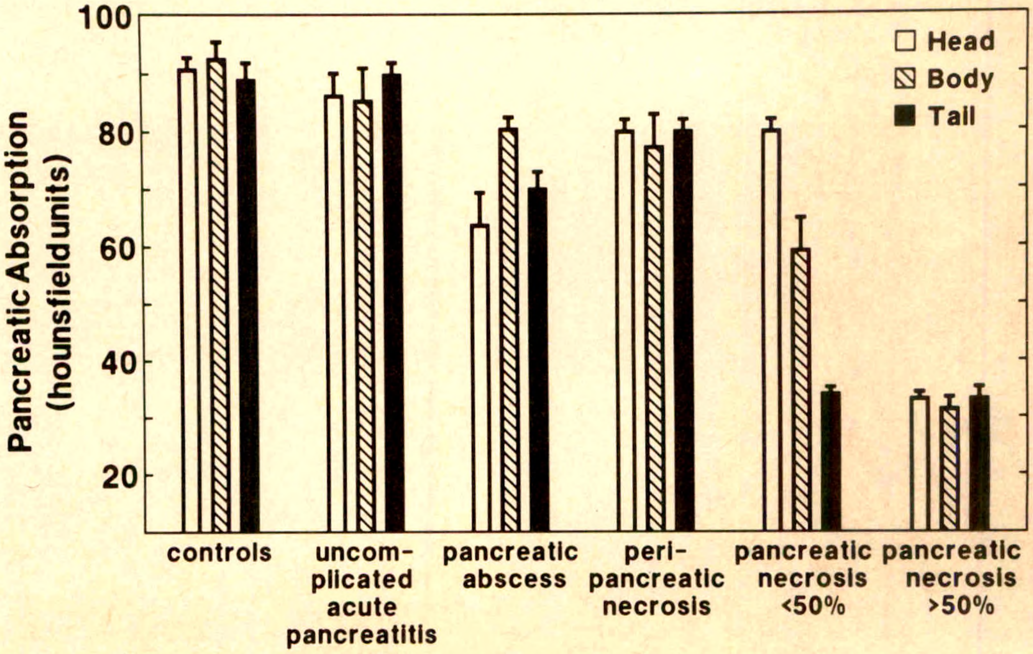
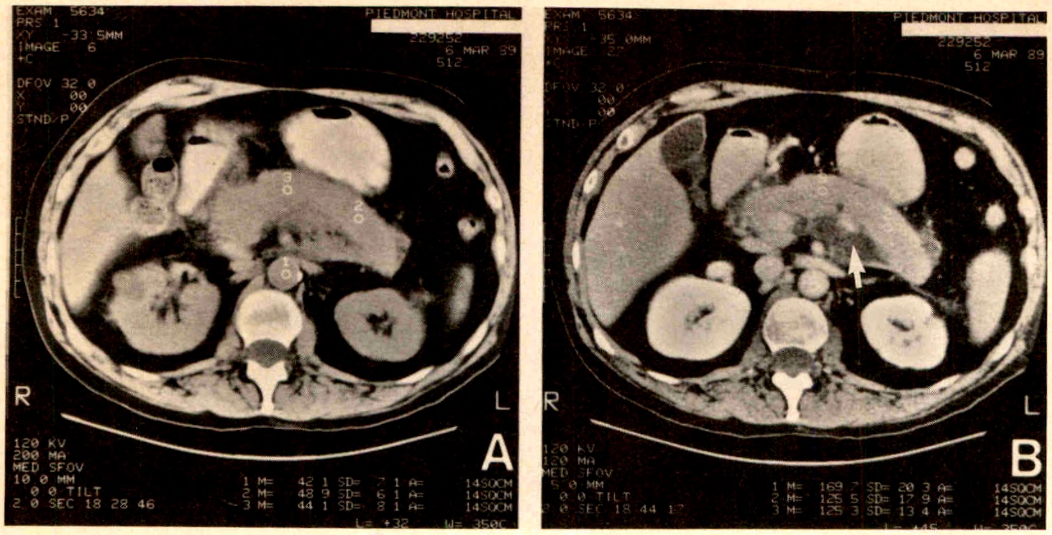


FIG. 2. Segmental pancreatic contrast densities in the control and study groups (average number of Hounsfield units + SEM).



FIGS. 3A and B. Uncomplicated acute pancreatitis. (A) Note marked swelling of the gland with bilateral pararenal space involvement. (Aortic density 42.1 HU, tail of pancreas 48.9 HU, body of pancreas 44.1HU) (B) Note uniform enhancement of pancreatic parenchyma during dynamic phase (125.5 HU, 125.3 HU), and delineation of retropancreatic inflammation (arrow) (pancreas: aorta ratio, 74%).

portantly the postcontrast pancreas:aorta ratio was less than 30% in each segment of pancreas subsequently proved to be necrotic by histology.

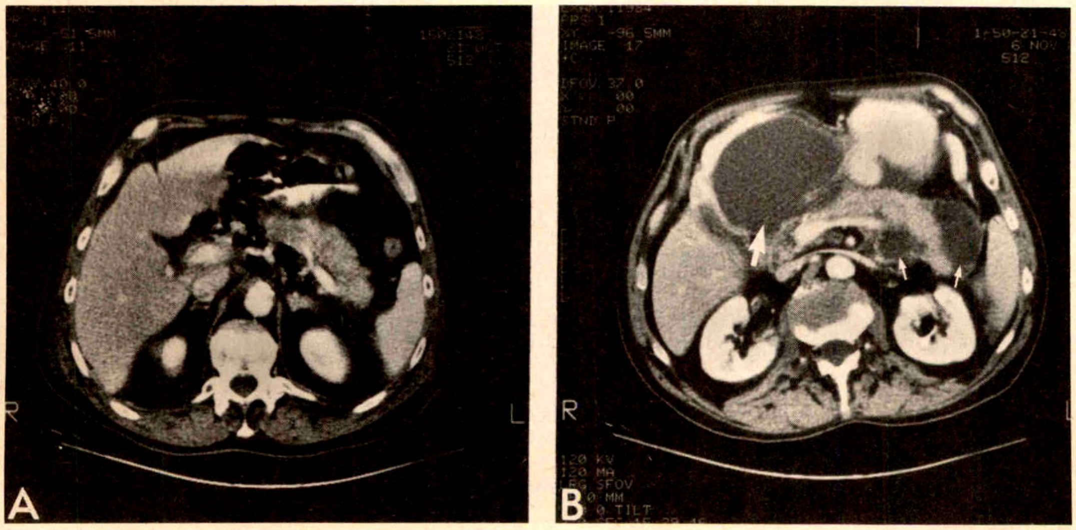
Of additional interest was the observation that average pancreatic parenchymal enhancement was correlated with the clinical severity of presentation; as the number of Ranson signs increased, postcontrast pancreatic parenchymal density decreased. The inverse correlation between Ranson's signs and the postinjection pancreas:aorta ratio was highly significant ($p < 0.001$).

There were no significant differences in postcontrast pancreas:aorta ratios between patients given the rapid intravenous bolus (5 seconds) and those given contrast during 40-to-80 second intervals.

No untoward reactions were noted in any of the 42 patients undergoing dynamic pancreatography. Despite prestudy concern no increases in serum creatinine occurred in any patient as a result of the large contrast load. However it is important to note that none of these patients underwent dynamic pancreatography in a volume-depleted state, and that similar results in regard to renal function might not be obtained if hypovolemia had been present.

Discussion

Recognition that pancreatic necrosis is the primary risk factor in the incidence of infectious complications in acute pancreatitis,[8] and that necrosis is also a principal determinant of overall outcome[6–8] has provided considerable impetus to the search for techniques capable of detecting parenchymal necrosis. Current methods for detection of pancreatic necrosis include meta-analysis of clinical features, various serum biochemical assays, and adaptations of pancreatic imaging techniques.



FIGS. 4A and B. Serial dynamic pancreatograms in a patient developing multiple pancreatic abscesses. (A) Only pancreatic swelling and pararenal involvement noted on first study (pancreas:aorta ratio, 64%). (B) Repeat study 2 weeks later shows three collections (arrows) that proved to be abscesses at surgery. Parenchymal enhancement remained uniform and normal (pancreas: aorta ratio, 63%).

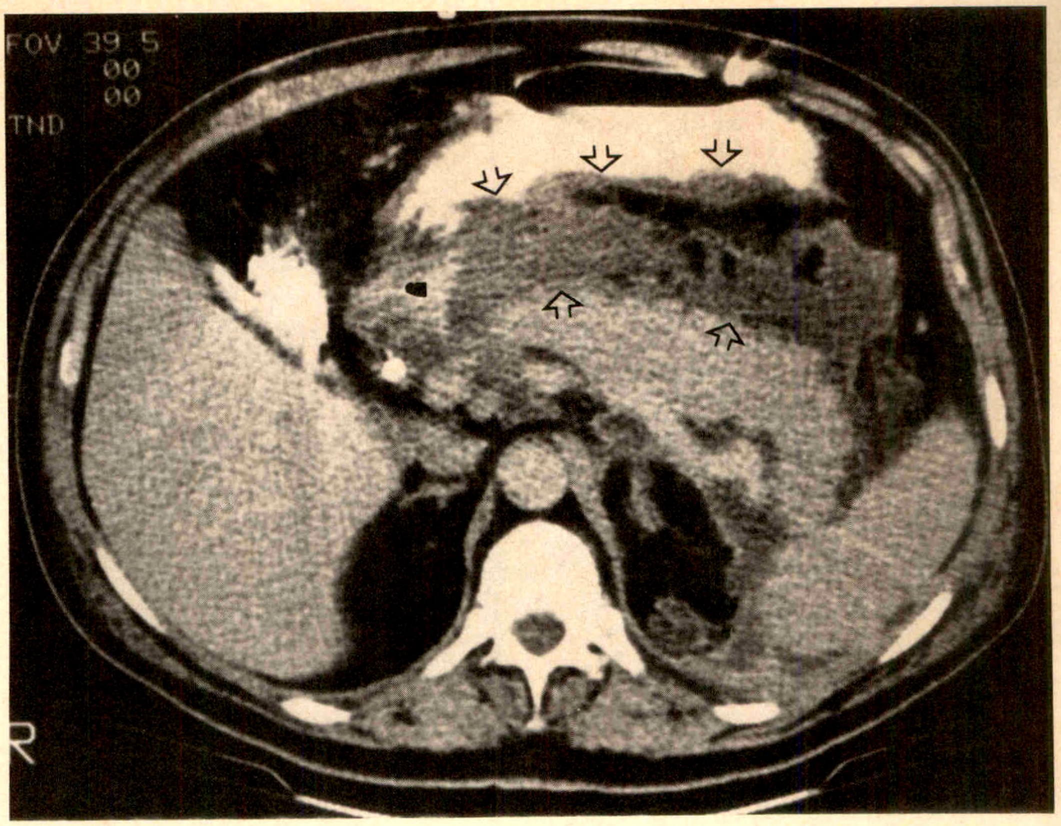
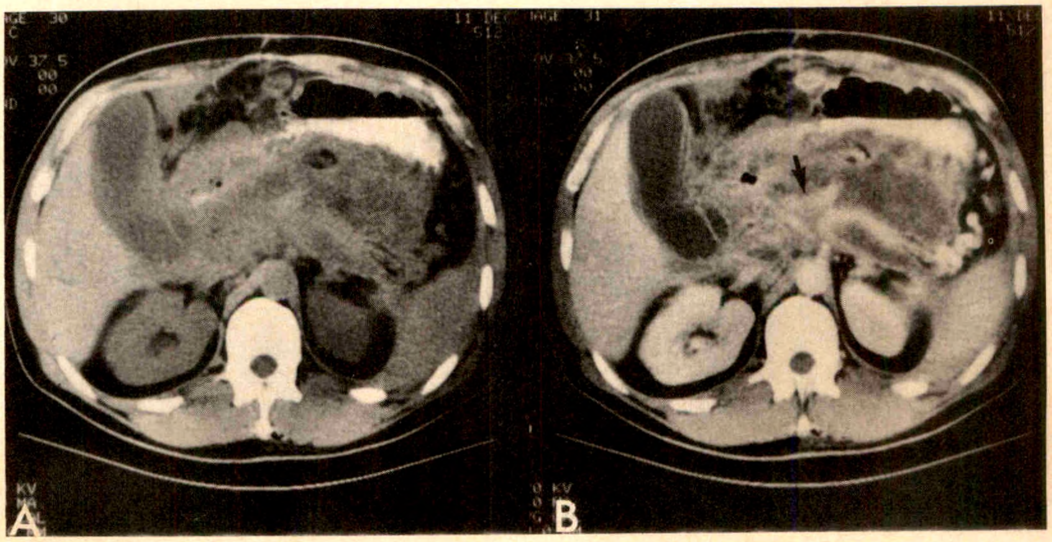


FIG. 5. Peripancreatic necrosis. Note well-enhanced pancreatic parenchyma (> 70 HU), but irregular borders of the gland. Extrapancreatic fat necrosis (arrows) is clearly seen.

In an extensive clinicopathologic analysis, Nordback and his coworkers found that the extent of pancreatic necrosis in glands resected for severe acute pancreatitis correlated poorly with fever > 38 C, abdominal distension, rebound, ileus, or even the presence of an abdominal mass.[10] In addition they were unable to correlate the degree of parenchymal necrosis with the leukocyte count, hematocrit, platelet count, blood glucose, or serum levels of Na, K, Ca, creatinine, bilirubin, triglycerides, or transaminases. Similarly Block and her coworkers found only a rough correlation between the number of Ranson signs and the presence of necrotizing pancreatitis.[11] Thirty-nine per cent of 93 patients undergoing pancreatic resection for necrotizing pancreatitis were initially classified as "mild" by Ranson criteria. Furthermore the histologic extent of pancreatic parenchymal necrosis cannot even



FIGS. 6A and B. Limited pancreatic necrosis. (A) Precontrast study is typical of a pancreatic "phlegmon." (B) After intravenous contrast, only the head and neck of the pancreas are enhanced (arrow). The nonenhanced body and tail of the pancreas were found to be necrotic at surgery.

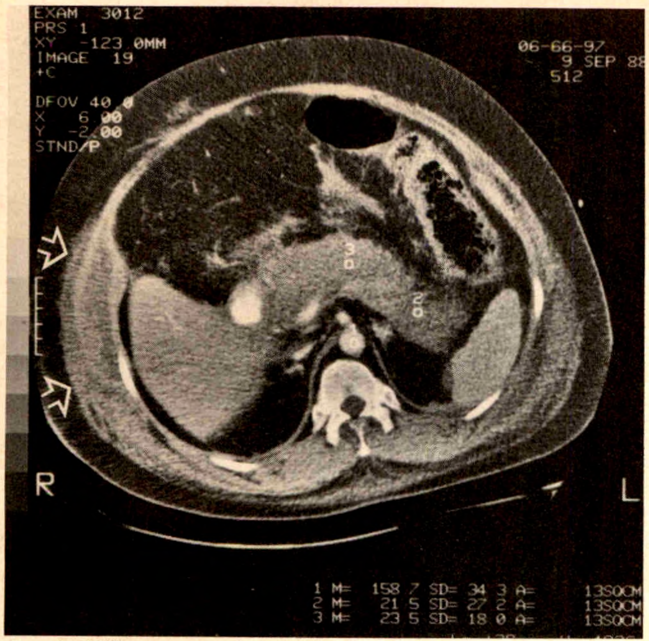

EXAM 3012
PRS 1
XY -123 0MM
IMAGE 19
+C
DFOV 40 0
X 6 00
Y -2 00
STND/P
06-66-97
9 SEP 88
512
R
L
1 M= 158 7 SD= 34 3 A= 13SQCM
2 M= 21 5 SD= 27 2 A= 13SQCM
3 M= 23 5 SD= 18 0 A= 13SQCM

FIG. 7. Diffuse pancreatic necrosis. No pancreatic parenchymal enhancement occurred with dynamic pancreatography (pancreas:aorta ratio, 14%). Note the markedly thickened abdominal wall musculature (arrows). This patient also had Grey-Turners sign (flank ecchymosis).

be predicted by the macroscopic appearance of the gland at surgery.[6,10] Despite several observations that the presence of turbid or hemorrhagic ascitic fluid suggests necrotizing pancreatitis,[10,12] a disturbing number of false negatives and false positives effectively invalidates sole reliance on any of these clinical approaches for the detection of pancreatic necrosis in the individual patient.

Intensive efforts have also been directed toward finding a reliable serum test for detecting pancreatic necrosis. Poly-(C)-specific ribonuclease (RNAse) has been claimed to be highly sensitive for detecting necrosis of pancreatic cells.[13] However the biomechanical analysis has been cumbersome, the test invalidated by deteriorating renal function (a common occurrence in severe acute pancreatitis), and to date, confirmation from other laboratories has been lacking. In a retrospective clinicopathologic study of 35 patients undergoing pancreatic resection for severe acute pancreatitis, Büuchler and his coworkers monitored a number of serum acute-phase reactants and found that specifically abnormal levels of α 1-antitrypsin could have correctly identified parenchymal necrosis in 77% of patients, α-2 macroglobulin in 85%, and C-reactive protein in 95%.[14] In a prospective study from our institution, however, we found that although recommended "predictive" values of these acute-phase reactants were present in 30 of 45 consecutive patients with acute pancreatitis, 22 of the 30 patients with serum values "predictive" for pancreatic necrosis had uncomplicated hospital courses (unpublished data). Abnormal values of α 1 antitrypsin, α 2 macroglobulin, and C-reactive protein may, therefore, be overly sensitive for detection of pancreatic necrosis and cannot be used prospectively as indicators for surgery. The role of serum complement factors (C_3, C_4) in detecting pancreatic necrosis has also been controversial. Foulis et al.[15] observed persistently low levels of C_3 and C_4 in patients dying from necrotizing pancreatitis, while values in patients who recovered returned to normal. Buchler[14] and his coworkers reported persistent depression of C_3 and C_4 values in patients with pancreatic necrosis, with an overall detection rate of 74% and 79%, respectively. On the other hand, Whicher[16] and his colleagues could not demonstrate any correlation between serum complement values and clinical outcome from acute pancreatitis. We may conclude that, as yet, none of the serum tests for detection of pancreatic necrosis has demonstrated accuracy or clinical reliability sufficient for use in the individual patient.

A variety of imaging techniques for identifying pancreatic necrosis have been proposed. However both Indium 111-labeled leukocytes,[17] and abdominal sonography,[18,19] have proved incapable of distinguishing between pancreatic parenchymal necrosis and edema. Even though computed tomography reliably demonstrates extrapancreatic inflammation in acute pancreatitis, and is accurate in detecting fluid collections (abscesses and acute pseudocysts),[2,20,21] and although these extrapancreatic changes can be correlated with clinical severity and outcome,[2,20] noncontrast CT has not been capable of distinguishing between edema and necrosis within pancreatic tissue.[2,21–23] Results from the current study confirm these observations. Noncontrast high density parenchymal lesions may represent blood,[24] or fluid with a high protein content.[25] Low density lesions may represent fat,[23] fluid,[2,23,26], tissue edema,[21,27] or necrosis.[21,25,28] Because therapeutic options depend on the specific pathologic process in the gland and can range from continued observation to extensive retroperitoneal debridement and open packing, accurate characterization of the existing parenchymal pathology is of critical importance.

In 1983, Kivisaari[29] and her coworkers observed that pancreatic parenchyma failed to enhance after rapid intravenous contrast infusion in eight of eight patients with subsequently proved pancreatic necrosis. In a prospective study the next year, they identified 2 groups of patients with acute pancreatitis using intravenous bolus, contrast-enhanced CT, 10 patients with low parenchymal enhancement (<30 HU), and 10 patients with normal enhancement (< 40 HU). Necrotizing pancreatitis was demonstrated at surgery in each of the patients with low enhancement, while all ten patients with normal enhancement were treated supportively and recovered without complication.[30] Furthermore when patients were combined from the first and second studies, mean contrast enhancement values for the 18 patients with necrotizing pancreatitis were significantly lower than the values for the 30 patients with presumptive acute edematous pancreatitis ($p < 0.01$).[30] The intravenous contrast bolus was well tolerated by all 48 patients.

The ability of intravenous bolus, contrast-enhanced CT scanning to detect pancreatic necrosis has been confirmed by other workers. Maier[22] has reported a sensitivity of 0.87 and a specificity of 1.0 for dynamic pancreatography in distinguishing between necrotizing pancreatitis in 63 patients undergoing surgery and 45 cases of "edematous pancreatitis" managed conservatively. No allergic reactions or deterioration in renal function occurred. As a result of failure of the pancreatic parenchyma to enhance, Larvin and his coworkers also correctly identified a group of eight patients with necrotizing pancreatitis from 31 patients with severe acute pancreatitis.[31] Finally Partanen et al.[32] reported significantly less contrast enhancement in 11 patients with necrotizing pancreatitis compared to 20 patients with non-nectrotizing acute pancreatitis. However we could not identify any previous reports studying dynamic pancreatography in normal controls, or in patients with complications of acute pancreatitis other than parenchymal necrosis.

In this study we have demonstrated that dynamic pancreatography is capable of distinguishing between patients with parenchymal necrosis and those with uncomplicated acute pancreatitis. Furthermore it would appear that an accurate clinical distinction can be made between the various other complications of acute pancreatitis using dynamic pancreatography. Parenchymal necrosis is apparently not a prominent feature of uncomplicated acute pancreatitis, pancreatic abscess, or peripancreatic fat necrosis. This latter observation has far-reaching therapeutic implications because selection of an appropriate therapy is dependent on an accurate clinical diagnosis.

With the addition of the current report to the rapidly growing data base on dynamic pancreatography, it seems reasonable to suggest that this technique should be used early in the course of those patients with severe acute pancreatitis (three or more Ranson signs), and in those cases with prolonged or otherwise complicated clinical courses.

The technique of dynamic pancreatography and data analysis differs somewhat in the current study from previous reports. While the total contrast load is 100 to 200 cc in all dynamic studies, the rate of administration varies. In the Finnish studies,[29,32] the total contrast load was given over 7 to 8 seconds. Such rapid administration produces higher enhancement values, but also more rapid tissue diffusion of contrast. Because we did not observe any significant differences in pancreas:aorta ratios as a function of the rate of contrast injection, we, as well as others,[22,31] prefer administration of a larger amount of contrast over a longer time, resulting in a longer parenchymal phase for analysis.

Despite variations in contrast injection rate, decreased or absent parenchymal enhancement in patients with necrotizing pancreatitis has been observed by all previous investigators. Because this observation seems secure, objective guidelines for identification of parenchymal necrosis must be established. While we, as well as others,[22,29,32] have consistently observed postcontrast parenchymal density values of < 40 HU in patients with necrotizing pancreatitis, variations in blood volume, pancreatic blood flow, contrast load, and patient geometry may make interpretation of an absolute value problematic. To limit variables between patients, we have preferred to use a dimensionless number, the result of comparing pancreatic parenchymal enhancement to aortic enhancement (pancreas:aorta ratio) as a form of internal control.

How does dynamic pancreatography recognize parenchymal necrosis? After experimental intravenous bolus injection, contrast agents have been shown to spread rapidly throughout the extracellular space.[33] Diffusion of iothalamate meglumine from the pancreatic microcirculation is aided by its low molecular weight (809 Daltons), and by the increase in capillary permeability known to be associated with acute pancreatitis.[34] These observations account for the observed enhancement of pancreatic parenchyma in non-necrotizing acute pancreatitis.

On the other hand, necrotizing pancreatitis is characterized by a severe reduction in pancreatic blood flow and perfusion,[35] with capillary flow particularly affected.[36,37] The loss of capillary flow in necrotizing pancreatitis is primarily due to microvascular endothelial damage and resultant thrombosis of nutrient vessels.[38,39] Due to the absence of collateral circulation at this distal level, little (if any) contrast material is presented to the capillary for diffusion, with a corresponding failure of enhancement.

Data exist to support this hypothesis. Microangiographic studies in pigs with acute edematous pancreatitis demonstrate that normal intravenous contrast enhancement is associated with an intact microcirculation. When necrotizing pancreatitis is produced, however, contrast enhancement is significantly reduced, and marked capillary disruption along with thrombosis and poor filling is consistently observed.[40] That absence of parenchymal contrast enhancement in the presence of pancreatic necrosis is due to microcirculatory obstruction, and not to hypoperfusion secondary to hypovolemia, has been clearly demonstrated in a porcine model.[41] Even more persuasive, however, are recent observations in humans of a direct correlation between the extent of pancreatic microcirculatory disruption, the degree of necrotizing pancreatitis, and the failure of the pancreatic parenchyma to be enhanced.[42] In brief, enhancement of pancreatic parenchyma by contrast agents seem to depend on an intact microcirculation. Parenthetically the principle of using parenchymal enhancement as a measure of microcirculatory flow may well have application in other fields of surgical interest, such as determining organ viability in transplantation or trauma, as well as in the diagnosis of mesenteric infarction.

If dynamic pancreatography proves to be capable of noninvasive prediction of pancreatic necrosis, how should this information be used? A thorough discussion of whether necrotizing pancreatitis should be resected as soon as it is recognized as advocated by some workers,[7,8,43] or whether noninfected pancreatic necrosis should be managed conservatively as suggested by others,[44–46] is beyond the scope of this paper. Indeed dynamic pancreatography may serve to resolve this conflict in the future. At the very least, however, because pancreatic necrosis is now known to be a principal determinant of complications and even of ultimate survival from acute pancreatitis, recognition of the development of pancreatic necrosis by dynamic pancreatography should alert the clinician to an escalation in risk and heighten anticipation of potential future complications.

Acknowledgments

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DISCUSSION

DR. CHARLES F. FREY (Sacramento, California): Dynamic pancreatography delineates the extent and site of pancreatic necrosis, information that is fundamental to the prognosis and clinical management of patients with acute pancreatitis.

Importantly this assessment of necrosis can be performed the day of hospital admission. In contrast many of the signs of severity of Ranson, Banks, and Imrie that we have come to rely on are not available until 48 hours after hospital admission, nor are their signs specific prognosticators of the presence or absence of necrosis or infection of the pancreas.

What are some of the applications of dynamic pancreatography? I will discuss three.

First, it facilitates the early diagnosis of infection. Approximately one half of the patients with significant amounts of necrosis will become infected. Further the greater the extent of pancreatic necrosis, the greater the likelihood of infection developing. Therefore dynamic pancreatography defines a group of patients at risk of developing infected pancreatic necrosis the day they enter the hospital. These patients require close follow-up. If infection is suspected, the area of necrosis can be aspirated under CT scan guidance, as advocated by Banks and Gerzoff and the returns gram stained and cultured. If infection is identified, almost every one agrees, operative debridement should be instituted promptly.

Second, dynamic pancreatography predicts pseudocysts. (Slide) This CT scan with IV bolus enhancement was performed on a woman with necrotizing pancreatitis involving the body of the pancreas but preserving the tail of the gland. As you can see on the CT scan, the tail is functioning. There is, however, no place for the fluid to go because the body of the pancreas is necrotic, so the fluid accumulates. We were able to predict in this woman on the day of admission that if she didn't develop infection of the necrotic portion of the pancreas, she would be at high risk of developing a pseudocyst, which she did 6 weeks later.

Third, dynamic pancreatography provides an opportunity to assess the value of different treatment protocols using patients with comparable degrees of pancreatic and peripancreatic necrosis. The CT scans with bolus enhancement of two patients show virtually total pancreatic necrosis. The first is this CT without enhancement (Slide), the second shows total, almost virtually total necrosis with enhancement.

This is another patient with almost total pancreatic necrosis.

We have been observing these patients with necrosis, even those with virtually total necrosis, and only operating if the clinical picture of hemodynamic or pulmonary failure or sepsis intervened or CT scan-guided aspiration of the area of necrosis demonstrated the presence of bacterial infection. We have not, nor have others, done well with this group of patients with more than 50% necrosis. Dynamic pancreatography provides an opportunity to identify this high-risk group of patients and evaluate new treatment protocols.

DR. JOHN H. C. RANSON (New York, New York): Dr. Bradley's report is, I believe, the first one in this country confirming the extensive observations in Finland and in Germany concerning the relationship between findings on contrast-enhanced CT and the presence of pancreatic necrosis.

In acute pancreatitis, tests can be used for predictive and also for diagnostic purposes. The prognostic signs that Dr. Bradley and Dr. Frey refer to were intended to identify, early in their disease, patients who have a high risk of life-threatening complications. Although they were not specifically intended to identify those with a high risk of local pancreatic complications, there is a relationship between these signs and late sepsis.

Computed tomography for the first time allows reasonably good noninvasive imaging of the anatomy of the pancreas and peripancreatic tissues. As we have reported in the past, early findings on CT help identify patients with a high risk of late pancreatic sepsis. They are usually not, however, diagnostic. In the present study, the addition of contrast enhancement to routine noncontrast CT identified six patients with pancreatic necrosis, but apparently did not help with the identification of 11 other patients who had abscesses or peripancreatic necrosis.

The assumption has been, and Dr. Bradley stated this, that it is the presence or absence of necrosis of the pancreas itself that determines the outcome of acute pancreatitis, and from my perspective, this may be the case, but it is still unproved. I think it may be the extent of pancreatic and peripancreatic necrosis and whether secondary infection supervenes that determines the outcome.

We are now reviewing a group of more than 80 patients with acute pancreatitis who underwent contrast-enhanced CT studies of the kind that you have heard about here. Six of this group were judged to have nonenhancement of 30% to 50% of the gland and three, or one half of this particular group, required operation for pancreatic sepsis. Three, however, recovered without any form of intervention at all. Eleven patients had nonenhancement of 50% or more of their gland and all of these patients required surgery, but nine required surgery for sepsis and two, as Charlie Frey has said, evolved to pseudocyst. They never became infected.

In terms of the sensitivity of contrast-enhanced CT in our patients, 14 of 20, or 70% of patients who required operation for sepsis or pseudocyst, had nonenhancement of 30% or more of their gland. Thus lack of pancreatic enhancement on contrast CT in our experience, as in that of Dr. Bradley, indicates a high probability of local complications, certainly if 50% or more of the gland does not enhance. However, as in Dr. Bradley's study, enhancement of the pancreas on contrast CT does not exclude the development of life-threatening late complications. In our study 17 patients developed infection of pancreatic or peripancreatic necrosis. Two of these patients, or 12%, died. Eleven had nonenhancement of the pancreas with a mortality rate of 9%, but the six who had enhancement had a mortality rate of 17%. Those patients who did not become infected did not die, despite the extensive nonenhancement.

Therefore, are you, Dr. Bradley, indeed willing to make therapeutic decisions based on the finding of nonenhancement of the pancreas that would not be dictated by the other clinical or radiographic findings?

Second, why do you choose to express the degree of nonenhancement by estimating the average density of the pancreas after contrast rather than by estimating the percentage of unperfused gland as others have done?

PROFESSOR M. TREDE (Mannheim, Germany): Coming from a surgical clinic in Germany where, in fact, we have for some time been investigating each case with acute pancreatitis with angiographic bolus—CT scan, I have a couple of questions.

First, as you all realize, the course of acute pancreatitis is like a film, and all you do with this investigation is to take one snapshot of one moment. When do you do your first examination, and how often do you repeat it, and why?

The second question has already been asked. What do you, in fact, do with the patient whose dynamic CT scan shows patchy malperfusion, but the patient sits up in bed smiling at you, is afebrile, and has a soft abdomen?

You know what I mean: we have the feeling that these CT scan findings lag behind the clinical picture. We have several well- documented cases in which, in fact, malperfusion is shown in the pancreas but the patient is already well on the way to recovery.

DR. LEWIS MATTHEW FLINT, JR. (Buffalo, New York): I would like to ask one question. One of the big disappointments of CT scanning in evaluation of abdominal trauma has been the amount of experience of the radiologist that is necessary for dependable results, and while the illustrations that Ed Bradley showed are pretty clear, I would like to ask how much input from the radiologist is necessary, and how much reliability is there from radiologist to radiologist.

DR. EDWARD L. BRADLEY (Closing discussion): To respond to Dr. Flint, because we developed our particular technique first and then interested the radiologists, we kept it relatively uncomplicated. By using a pancreas:aorta ratio, the technique is not user-sensitive, and is therefore exportable. Also the basic concept of using dynamic studies as measures of microcirculatory flow seems quite applicable to other organ systems and conditions.

Several of the discussants have asked whether we use dynamic pancreatography to make clinical decisions. Yes, we do. The fact that pancreatic necrosis can be correlated with severity in acute pancreatitis means that when pancreatic parenchymal necrosis is demonstrated by dynamic pancreatography, important prognostic information for that individual patient is generated. In contrast, clinical prognostic criteria are only 50% to 60% sensitive for severe pancreatitis in individual patients. Furthermore, knowing pancreatic necrosis is present heightens our anticipation of the possibility of secondary infection of the necrosis. In this sense, dynamic pancreatography serves as an early warning system. We agree with Professor Trede and Dr. Ranson that we would not subject a patient to surgery on the basis of the dynamic pancreatogram alone.

When do we perform dynamic pancreatography? Now that our controlled study is completed, we reserve admission dynamic pancreatography for those patients who are likely to have pancreatic necrosis: those appearing quite ill, or those exhibiting three or more Ranson signs. We do not believe DYNP is necessary for patients with mild pancreatitis. DYNP is also indicated in patients with initially mild disease who subsequently become ill. We repeat it on a weekly basis until the clinical course has been established.

Dr. Frey, thank you for sharing your experiences with dynamic pancreatography with us. We are comforted by your similarly favorable experience.

Why did we do some of our calculations on the basis of average pancreatic density? Merely to establish the presence of a correlation between overall enhancement and severity. The values of clinical use for detecting pancreatic parenchymal necrosis are the segmental pancreas:aorta ratios.

It is important to appreciate that we are not talking about routine contrast-enhanced CT here. Dynamic pancreatography involves pressure injection of a large volume of contrast and specific time-density reconstructions. We anticipate that this safe technique will become increasingly valuable in the management of severe acute pancreatitis.

Relationship Between Colorectal Liver Metastases and CEA Levels in Gallbladder Bile

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While computerized tomographic (CT) scanning and intraoperative exploration are both considered accurate measures of liver involvement with metastatic disease, 10% to 30% of colorectal liver metastases remain undetected. Attempting to improve current methods for detecting colorectal liver metastases, CEA levels in gallbladder bile and serum from patients with known liver metastases were determined. One hundred per cent of patients with single and multiple metastases of various dimensions were observed to have gallbladder bile CEA levels strikingly higher than serum values (4.7 to 259 times greater, $p = 0.0009$). Linear regression analysis of estimated tumor volume and surface area *versus* gallbladder bile CEA levels predicted that very small tumors (≤ 1 cm^3 in volume) might produce detectable levels (9 to 41 ng/mL) of biliary CEA. For this reason, patients who lack clinical and radiologic evidence of distant metastases at the time of primary colorectal resection but who do have elevated gallbladder bile CEA levels (≥ 10 ng/mL) are being followed for the appearance of occult hepatic metastases.

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DESPITE CONTEMPORARY DIAGNOSTIC and therapeutic advances, liver metastases continue to be a significant obstacle to the curative treatment of colorectal cancer. Occult (undetected), synchronous liver metastases are believed to be present in 10% to 30% of patients at diagnosis of primary colorectal cancer.[1-7] Because 25% to 30% of liver metastases may be resected for cure, the need for improved, earlier methods of detection for these occult lesions is evident.[8-10] Likewise patients with occult metastases may benefit from effective chemotherapy. Currently computerized tomographic (CT) scanning, liver scintiscan, and ultrasound are reported to have an accuracy rate of 80% or more for detecting liver metastases of various sizes. Unfortunately, however, lesion-by-lesion analyses in prospective studies have failed to demonstrate reliable accuracy in the detection of tumors less than 3 cm in diameter (or a volume equivalent to 14.1 cm^3).[11,12] This limitation is further emphasized by recent clinical studies in which surgical exploration documented that preoperative CT scans can define the number and location of lesions in less than 43% of cases.[13] CT scans are also frequently imprecise in distinguishing between benign and malignant primary or metastatic liver lesions.

Carcinoembryonic antigen (CEA) is the most sensitive immunological marker for colorectal liver metastases. Postoperative serum CEA analysis is a reliable monitor for early detection of recurrent local and/or metastatic colorectal cancer.[14] Preoperative serum CEA levels, however, are often inaccurate indicators of metastatic disease. As many as 50% of patients without evidence of metastatic disease have abnormal CEA levels before resection of the primary lesion.[15,16] Furthermore a significant number of patients may have liver metastases detectable by CT scanning in the face of marginally elevated or normal serum CEA levels.[13] Therefore surgical exploration has been required in most patients to accurately quantify and localize metastatic lesions.

Analysis of serum from peripheral blood may not accurately reflect or detect the localized production of CEA in the liver by metastatic tumor. Gallbladder bile CEA levels might be a more sensitive index of colorectal liver metastasis. This novel hypothesis was based on several rationales. First tumor cell-derived products like CEA

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should have higher concentrations in the smaller biliary pool than the larger serum pool. Second bile produced by hepatocytes is exposed to tumor cell products through either transhepatic receptor-dependent transport mechanisms or through paracellular mechanisms.[17] Finally we know that bile and associated constituent proteins may have a twelvefold concentration in the gallbladder.

The results presented here directly supported this hypothesis and have led to a pilot study using this technique as a means of identifying patients potentially at high risk for occult liver metastasis at the time of primary resection.

Methods

Gallbladder Bile and Serum Specimens

Gallbladder bile and serum samples were obtained synchronously from patients (study group) who underwent exploratory laparotomy for resection of colorectal cancer, hepatic resection, or intra-arterial infusion for metastatic colorectal cancer, and hepatic resection for benign or other malignant hepatic lesions. At the time of operation, serum samples of CEA were collected *via* peripheral venipuncture. In instances when the gallbladder was not removed, bile was obtained during operation by transhepatic gallbladder puncture. Control samples of CEA included patients undergoing "therapeutic" cholecystectomy for cholelithiasis (obstructed and unobstructed biliary tree) or "prophylactic" cholecystectomy performed at the time of gastric stapling for morbid obesity. Informed consent was obtained in accordance with the policy of the Institutional Review Board of the College of Medicine, University of Florida. Bile and serum samples were centrifuged (9000 × g, 10 minutes) and supernatants were aliquoted and frozen at −70 C until further analysis could be completed.

CEA Determinations

Serum samples were assayed without dilution using a sandwich solid-phase two-site mouse monoclonal antibody radioimmunoassay kit (Hybritech, Inc., San Diego, CA). Gallbladder bile samples required dilution to detect CEA content. Unlike serum, gallbladder bile contained inhibitory substances that affected the linearity of a standard dilution curve. Dilution of bile eliminated the effects of the inhibitor and allowed the detection of CEA by radioimmunoassay. Most bile samples with endogenous CEA values between 40 and 4000 ng/mL required dilution to approximately 1:40 with CEA-free serum to affect linearity of the dilution curve and accurately assess the CEA concentration of the samples. This is shown in Figure 1A, where endogenous CEA levels were determined in various dilutions (with CEA-free serum) of gallbladder bile from a typical patient with a solitary colorectal liver metastasis. Linearity of the dilution curve, depicting true levels of CEA (calculated as dilution factor X observed CEA level), was not reached until the bile was diluted to approximately 1:40. By comparison serum was observed to dilute in a linear fashion without evidence of inhibition (Figure 1B). To further establish the presence of an inhibitor in bile and the necessity for dilution, a known concentration (200 ng/mL) of exogenous CEA in serum was admixed 1:1 with normal gallbladder bile to obtain a final expected concentration of 100 ng/mL (Fig. 2). This mixture was then diluted with CEA-free serum and the linearity of the dilution curve was, once again, established only when bile had been diluted approximately fortyfold. Larger dilutions were required for samples with endogenous CEA levels > 4000 ng/mL in order for linear regression analysis to be accurately completed.

Alternatively bile samples with undetectable CEA levels by the dilution method (*i.e.*, endogenous levels < 40 ng/mL or levels < 1 ng/mL after dilution fortyfold) were assayed using a new technique that required acid extraction of bile samples before radioimmunoassay. Briefly samples were pretreated with 1.2 M perchloric acid followed by neutralization with 1.0 M Tris buffer (pH 10.5), dilution with 0.15 M phosphate-buffered saline, and ultrafiltration to separate CEA from interfering biliary substances. Solid-phase radioimmunoassay was then used to directly measure CEA values. Details of this procedure are reported separately.[18]

Statistical Analysis

Statistical analysis was done using the Statistical Analysis System, Cary, NC. A paired, two-tailed t test was used to compare the means of sample differences for two groups (serum and bile CEA levels).

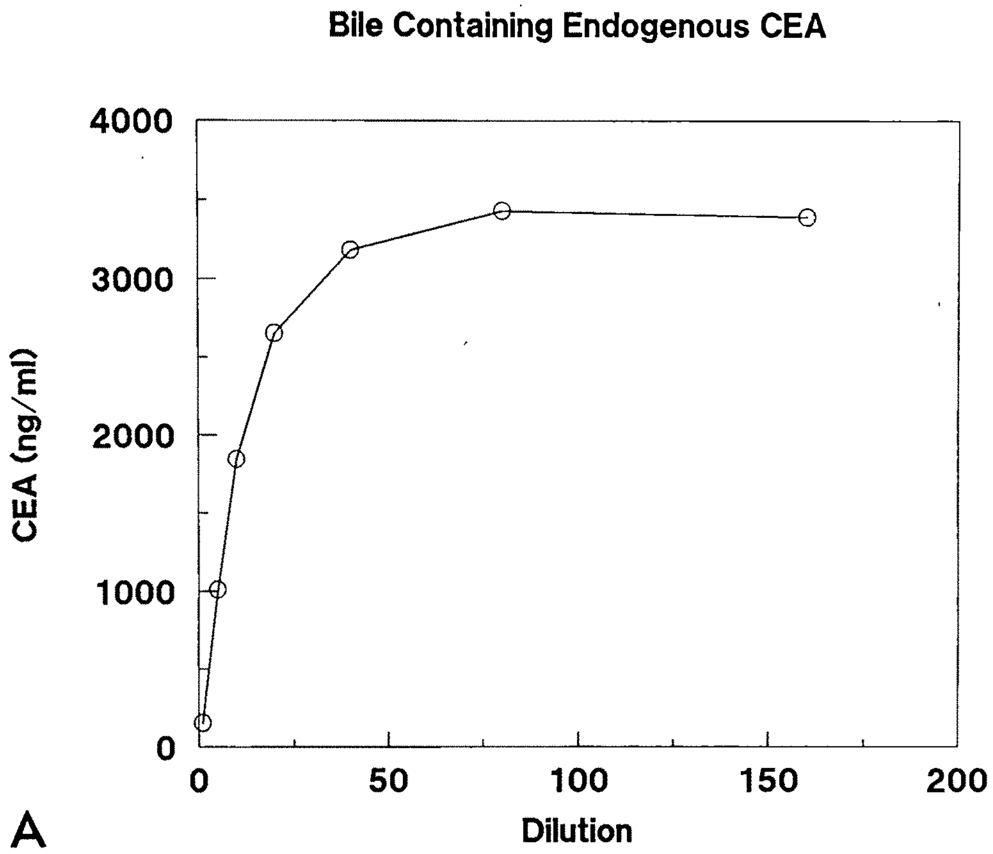
Results

Bile from Pathologically Normal Gallbladders

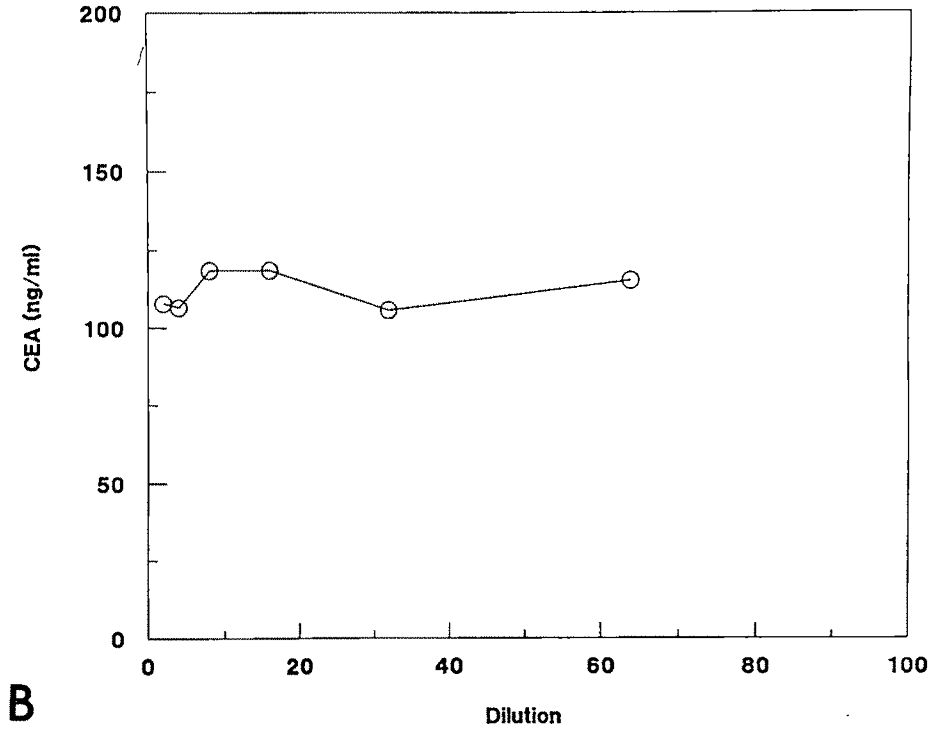
Bile obtained from seven patients with pathologically normal gallbladders and without evidence of biliary obstruction produced normal CEA levels ≤ 0.5 ng/mL (Table 1). Simultaneously drawn serum CEA levels were also essentially normal.

Biliary CEA Levels in Obstructed Bile

Sampling of gallbladder and common duct bile from patients with biliary tract disease was done to determine if false-positive results might occur in a patient with biliary tract pathology. As seen in Table 2, patients with cholelithiasis (patients 8 to 10) and/or choledocholithiasis (patient 11) but no evidence of cystic duct obstruction had normal bile CEA levels with low or normal serum CEA levels. Patients diagnosed with acute cholecystitis second-



Dilution of CEA Serum Standard (100 ng/ml)



FIGS. 1A and B. (A) CEA levels were determined on gallbladder bile from patient 35 (Table 4) after dilution from 1:1 to 1:150 using CEA-free serum. Linearity of the dilution curve was not obtained until the bile was diluted approximately forty-fold. (B) Dilution of serum samples did not alter amount of CEA measured. Serum samples, unlike bile samples, do not contain inhibitory substances that interfere with CEA analysis.

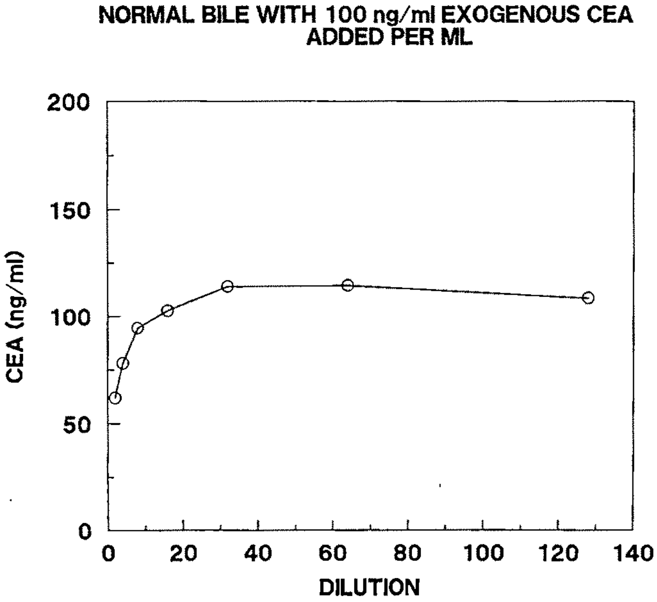


FIG. 2. Accurate estimation of CEA levels in normal gallbladder bile with CEA added exogenously requires fortyfold dilution before analysis.

ary to cystic duct obstruction (patients 12 and 13) had elevated levels of CEA in their gallbladder bile while normal levels were simultaneously observed in unobstructed common duct bile from the same patients (patients 12a and 13a). Similarly one patient (14) with acalculus cholecystitis and cystic duct obstruction from sludge had elevated CEA levels in the bile. Common bile duct obstruction with (patients 16 and 17) or without (patient 15) an associated inflammatory process also led to elevated bile CEA levels.

TABLE 1. *Analysis of Serum and Gallbladder Bile CEA Levels from Controls (Normal Gallbladders)*

		CEA Levels (ng/mL)*	
Patient	Diagnosis	Serum	Bile
1	Morbid obesity†	0.0	0.2
2	Morbid obesity	2.7	0.0
3	Morbid obesity	0.0	0.0
4	Morbid obesity	—	0.0
5	Morbid obesity	1.5	0.5
6	Morbid obesity	—	0.5
7‡	Morbid obesity	0.0	0.0

* In this and other tables, CEA levels are a mean of two or more determinations per sample. Bile CEA levels were determined by dilution method and by perchloric acid extraction method. See materials & methods.

† Gallbladders were removed prophylactically during gastric partitioning procedures to prevent future cholelithiasis related to loss of weight primarily as fat mass.

‡ Throughout remaining tables patients will continue to be numbered consecutively.

TABLE 2. *Analysis of Serum and Gallbladder Bile CEA Levels from Controls (Biliary Pathology)*

		CEA Levels (ng/mL)	
Patient	Diagnosis	Serum	Bile
8	Cholelithiasis, patent CD*	0.1	0.7
9	Cholelithiasis, patent CD	4.4	2.2
10	Cholelithiasis, patent CD	0.7	0.7
11	Cholelithiasis, choledocholithiasis, nondilated CBD,† patent CD	—	0.0
12	Acute cholecystitis	3.3	19.2
12a	Acute cholecystitis (CBD bile)		1.0
13	Acute cholecystitis	2.1	160.0
13a	Acute cholecystitis (CBD bile)		0.0
14	Acalculous cholelcystitis, sludge‡	2.0	11.3
15	Cholelithiasis, choledocholithiasis, dilated CBD, patent CD	0.0	22.6
16	Acute cholecystitis, gallstone, pancreatitis, CBD obstruction	1.7	53.2
17	Acute cholangitis (CBD bile)	—	134.0

* CD, cystic duct.

† CBD, common bile duct.

‡ Cystic duct obstructed.

Biliary CEA from Livers with Lesions Not of Colorectal Origin

Patients with benign and malignant hepatic lesions not of colorectal origin (Table 3) such as breast cancer metastases, hemangioma, and hamartoma had no elevation of CEA in serum or gallbladder bile. Patient 21 with a hepatoma, a known source of CEA, had high levels of biliary CEA despite low serum levels.

Biliary CEA from Livers with Metastases of Colorectal Origin

All patients with colorectal liver metastases had elevated levels of CEA in their gallbladder bile (Table 4). The extent of CEA accumulation in the bile can be demonstrated in the bile:serum ratio of these patients. The lowest ratio (4.7) was seen in patient 28 and the highest (259) in patient 35. The remaining 15 patients in this group had easily detectable gallbladder bile CEA levels ranging from 120 to 59,237 ng/mL. A paired t test comparing mean serum

TABLE 3. *Analysis of Serum and Gallbladder Bile CEA Levels from Controls (Hepatic Lesions)*

		CEA Levels (ng/mL)	
Patient	Diagnosis	Serum	Bile
18	Breast cancer metastases	0.5	0.8
19	Hemangioma	0.0	0.0
20	Hamartoma	0.0	0.5
21	Hepatoma	2.3	712.0

TABLE 4. *Analysis of Serum and Gallbladder Bile CEA Levels from Patients with Metastatic Colorectal Cancer (Hepatic Lesions)*

		CEA Levels (ng/mL)		
Patient	Diagnosis	Serum	Bile	B/S Ratio
22	Solitary lesion 3.6 cm^3* (11.3 cm^2)†	15.2	120.0	7.9
23	Solitary lesion 9.2 cm^3 (21.2 cm^2)	13.7	585.6	42.7
24	Solitary lesion 25.8 cm^3 (42.1 cm^2)	59.3	789.6	13.3
25	Bilobar lesions‡ 28.3 cm^3 (54.2 cm^2)	45.2	331.3	7.3
26	Unilobar lesions‡ 28.7 cm^3 (52.1 cm^2)	4.6	246.3	53.5
27	Solitary lesion 31.1 cm^3 (47.8 cm^2)	2.4	190.0	79.2
28	Solitary lesion 31.5 cm^3 (48.3 cm^2)	124.5	584.0	4.7
29	Solitary lesion 94.9 cm^3 (100.6 cm^2)	38.7	3384.1	87.4
30	Solitary lesion 113.1 cm^3 (113.1 cm^2)	76.7	3558.1	46.3
31	Solitary lesion 508.4 cm^3 (307.9 cm^2)	394.8	4656.5	11.7
32	Multiple lesions	42.8	1616.0	37.8
33	Multiple lesions	8.9	312.0	35.1
34	Multiple lesions	18.5	2982.0	161.0
35	Multiple lesions	12.9	3336.0	259.0
36	Multiple lesions and primary tumor	25.9	2015.0	77.8
37	Multiple lesions and primary tumor	44.9	477.2	10.6
38	Multiple lesions	3600.0	59023.0	16.4

* Volume and †Surface Area determined from the mean of three pathologic measurements (length, width, depth) on resected specimens that were used to estimate a tumor radius. Tumors assumed to approximate spheres such that volume = 4/3 πr^3 and surface area = 4 πr^2.

‡ Volume and Surface area determined from sum of values for two lesions.

and bile CEA levels generated a p value of 0.0009 (patient 38 excluded from analysis secondary to large deviation from the mean).

Biliary CEA from Livers with Absence of Metastatic Lesions

Nine patients with primary gastrointestinal cancer and the absence of primary hepatic disease or hepatic metastases documented by preoperative CT or by exploratory laparotomy were included in this study to determine the potential sensitivity, specificity, and feasibility of detecting occult colorectal metastases. Gallbladder bile and serum samples were simultaneously obtained at the time of primary resection, and CEA determinations were done.

As seen in Table 5, gallbladder bile from seven patients with pathologic confirmation of colorectal adenocarcinoma was analyzed for CEA levels. Three of these specimens (from patients 41, 42, and 45) showed elevations of biliary CEA (> 10 ng/mL). Patients 46 and 47, with final diagnoses of leiomyosarcoma and mucinous cystadenocarcinoma, respectively, had either undetectable or extremely low levels of CEA in both serum and bile.

Linear Regression Analysis of Hepatic Tumor Volume and Surface Area Versus *CEA Levels in Bile*

Ten of the 17 patients (Table 4) with metastatic colorectal cancer underwent curative hepatic resections. Most hepatic lesions were spherical, and three-dimensional measurements of the tumor were made on the fresh specimens. Estimated volume and surface area were calculated (volume = 4/3 πr^3, surface area = 4 πr^2) and compared with CEA obtained from the gallbladder bile using linear regression analysis. As seen in Figure 3, extrapolation of linear regression analysis for tumor volume *versus* CEA (upper line) predicted a gallbladder bile CEA level of 41.7 ng/mL for a tumor volume of 1 cm^3. Similarly a CEA level of 8.9 ng/mL was estimated for a tumor surface area of 1 cm^2 (Figure 3, lower line). The Pearson correlation coefficient for linear regression analysis of tumor volume and surface area *versus* CEA levels in gallbladder bile was r = 0.8. This data suggests that tumors as small as 1 cm^3 could potentially be detected through CEA analysis of gallbladder bile and would likely produce a bile CEA level

TABLE 5. *Analysis of Serum and Gallbladder Bile CEA Levels from Patients with No Hepatic Lesions*

		CEA Levels (ng/mL)	
Patient	Diagnosis	Serum	Bile
39	Colorectal cancer	22.9	0.6
40	Colorectal cancer	1.9	0.6
41	Colorectal cancer	1.4	11.3
42	Colorectal cancer	50.1	15.5
43	Colorectal cancer	0.0	4.4
44	Colorectal cancer	0.7	0.4
45	Colorectal cancer	5.5	13.5
46	Leiomyosarcoma	0.0	0.0
47	Mucinous cystadenocarcinoma (appendix)	1.5	2.9

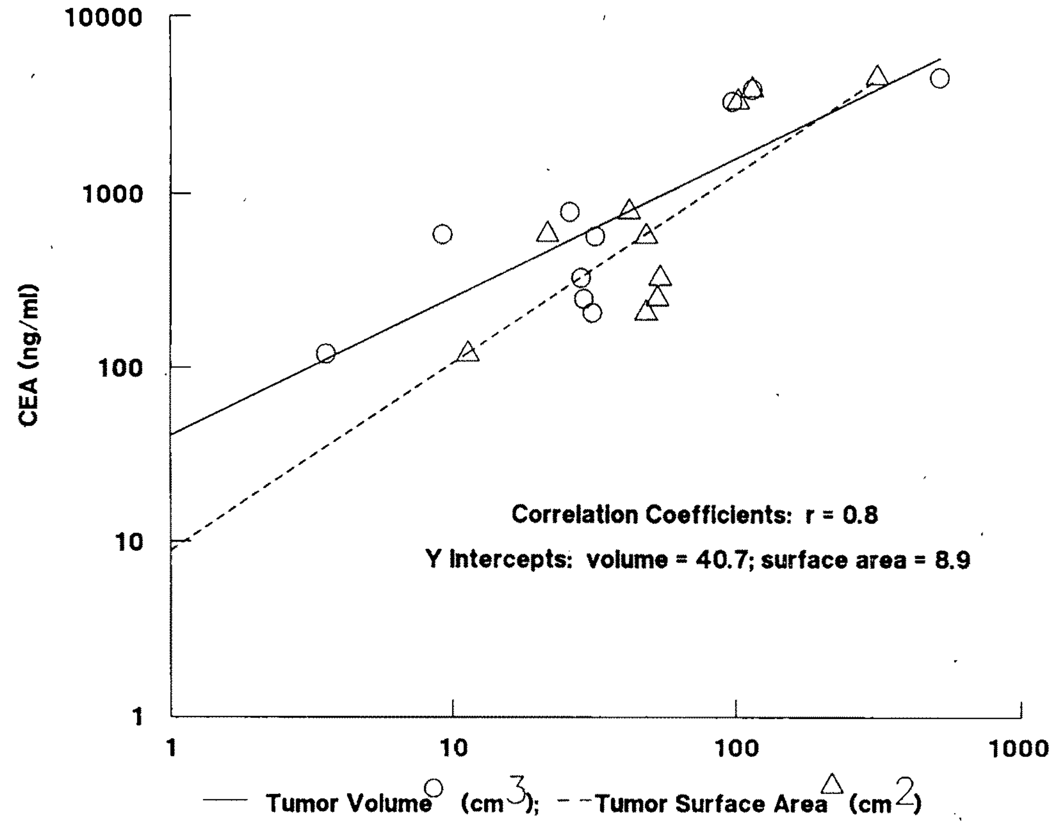


FIG. 3. Linear regression analysis comparing tumor volume (upper solid line) and surface area (lower dashed line) with gallbladder bile CEA levels (ordinate).

between 9 and 41 ng/mL. The actual value of CEA measurable in gallbladder bile possibly depends on a number of factors including extent of tumor necrosis and gallbladder bile concentration.

Discussion

Although analyzing fluids bathing gastrointestinal tumors for CEA content is not an entirely novel idea, we have proposed a unique application for CEA analysis.[19,20] The hypothesis that colorectal liver metastases could be accurately detected through measurement of CEA levels in gallbladder bile was confirmed by the finding that 100% of patients with documented colorectal liver metastases had significant elevations of CEA in gallbladder bile—up to 259 times greater than that in serum.

In the past attempts have been made to analyze duodenal aspirates for CEA content to predict the presence of pancreatic cancer and hepatic metastases from colorectal cancer.[21-24] These efforts, however, have been largely unsuccessful because the normal pancreas and gastrointestinal mucosa release significant amounts of CEA.[25-27] Similarly our efforts at analyzing duodenal aspirates were thwarted by frequent and unpredictable false-positive results. Analysis of gallbladder bile, however, produced false-positive results only in the presence of gallbladder disease. Acute inflammatory conditions (acute cholecystitis, cholangitis, gallstone pancreatitis) and biliary tree obstruction (cystic and/or common bile duct) were frequently associated with elevations of CEA. These nonspecific elevations may be related to immunologically cross-reacting biliary glycoproteins.[28] Chronic cholecystitis, cholelithiasis without cystic duct obstruction, and choledocholithiasis without common bile duct obstruction did not cause elevations of gallbladder bile CEA levels in the patients examined in this study; however, CEA values should be interpreted with caution in the presence of any gallbladder or biliary tree pathology.

Although hepatic clearance of serum CEA is high, biliary excretion of CEA is believed to be low.[29] Consequently significant elevations of biliary CEA should not commonly occur secondary to elevations in serum or plasma CEA from a primary tumor source. Experiments on rats and monkeys have shown that recovery of intravenously injected doses of CEA in hepatic and gallbladder bile is maximally 1% to 1.5% and 9%, respectively, of the administered dose.[29] The difference between hepatic and gallbladder bile levels may be related to the fact that the gallbladder can concentrate bile twelvefold. While human studies of biliary excretion of CEA are yet to be done, this observation is compatible with our findings that protein and bilirubin concentrations in hepatic and gallbladder bile may also differ by as much as twelvefold (unpublished observations).

All liver lesions of colorectal origin in this series produced CEA, despite several instances of normal-to-low levels of serum CEA. The possibility of obtaining false-negative results, however, from patients whose colorectal liver metastases do not produce CEA cannot be eliminated.

The new assay kits that use specific mouse monoclonal antibodies can better define the presence or absence of serum CEA levels as low as 1 ± 0.97 ng/mL. Using this monoclonal antibody system to analyze pretreated gallbladder bile samples, we confirmed the presence of metastatic liver tumors with volumes as low as 3.6 cm^3 (or 1.9 cm in diameter). Because gallbladder bile CEA levels are often quite high even in the presence of small metastatic foci, we predicted that patients bearing even smaller, clinically occult tumors might be identified. For this reason linear regression analysis of gallbladder bile CEA levels *versus* tumor volume and surface area was done. This analysis suggested that tumors as small as 1 cm^2 in surface area or 1 cm^3 in volume would produce detectable levels (9 to 41 ng/mL) of CEA in bile. The majority of occult lesions, however, are not small. In one study, only 3 of 70 patients had occult metastases $\leq$ 1 cm in diameter.[3] Subsequent analysis of gallbladder bile from seven of our patients with primary colorectal lesions and no evidence of metastasis at laparotomy or on preoperative CT scans identified three patients who have elevated biliary CEA levels. These three patients may harbor occult liver metastases. Only with further long-term follow-up of these patients and with prospective analysis of gallbladder bile from similar patients can this question be answered.

Both prognostic and therapeutic information might be obtained with early detection of occult hepatic metastases. A patient's candidacy for surgery would be established sooner and before invasion of structures contiguous to the liver parenchyma (diaphragm, inferior vena cava) or progression to a point (hepatic vein invasion or hepatic lymph node spread) when metastases to distant, tertiary sites are imminent. Patients identified at high risk for occult lesions could also be selected for earlier and perhaps more effective adjuvant therapy. The concept that adjuvant portal vein chemotherapy may be effective in the treatment of occult metastases has been supported by pilot prospective trials that have demonstrated some survival benefits from the technique.[1]

Gallbladder bile analysis may also allow the confirmation of questionable CT scan findings of hepatic metastases before exploratory laparotomy for possible hepatic resection. Gallbladder bile can be safely obtained through percutaneous, transhepatic CT- or ultrasound-guided aspiration, as use of the transhepatic route virtually eliminates the risk of bile leakage. Thus percutaneous sampling of gallbladder bile may permit preoperative confirmation of the diagnosis of metastatic colorectal cancer in situations in which lesions are too small for accurate radiologic assessment. This technique might also allow follow-up sampling of bile in patients identified at the time of primary colorectal resection to be at high risk for development of liver metastasis. Hepatic bile might also be obtained for similar analyses using endoscopically placed nasobiliary tubes that isolate the biliary tree from the proximal and distal gastrointestinal tract. This technology is under development and will provide the basis of a future communication.

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DISCUSSION

DR. FRANK G. MOODY (Houston, Texas): The authors have taken advantage of the concentrating function of the gallbladder to correlate the CEA levels in the gallbladder bile with hepatic metastases from colorectal cancer.

My question relates to the sensitivity of this methodology in patients who have colorectal tumors in place whom you are evaluating before or during operation. It seems to me that the presentation of CEA from a primary tumor would be in the portal system. Therefore it is conceivable that the concentration of CEA in the portal system might be high, and therefore, the CEA levels in gallbladder bile would be from the primary tumor rather than from an occult metastasis.

Also if one is to establish sensitivity, you must have something better than a preoperative CT scan. Clearly intraoperative ultrasound is a much more sensitive technique that could probably detect a 1-cm lesion. Finally I wish that the authors in closing would comment on what they do when they detect these very small metastases in the liver at the time of the primary resection of the tumor.

JOHN PETER MINTON (Columbus, Ohio): We have looked at CEA for a number of years. I think we need to realize that CEA tests are available to us, and depending on which laboratory our pathology departments obtain their CEA test kits from, some of the tests are monoclonal and some are polyclonal antibody test systems. This means that the test may be made from primary colon cancer tissue and other tests from liver metastasis. Sometimes different tests will give us different information as far as screening patients for tumors. Do you know if the antigen in your test was made from a primary colon cancer or metastatic disease to the liver?

It is possible that your technique may well become an important way to stage patients with resectable primary colon cancers. It is difficult to accurately clinically stage occult hepatic metastasis. A below-the-umbilicus midline incision permits only a limited manual examination of the liver, so I extend the incision up to the xiphoid, take down the falciform ligament, and do a careful bi-manual examination.

Ultrasound in conjunction with a bi-manual examination may help detect 1-cm lesions that can be removed easily. I have recently removed 18 lesions from both lobes of one liver. Several of the 5-year patients are free of disease. There have been no hospital deaths in a series of nearly 200 patients.

What will you do when you find an elevated CEA in the bile of a gallbladder aspirate? Will you wait until something shows up on the CT scan?

DR. TIMOTHY J. YEATMAN (Closing discussion): First I would like to address Dr. Moody's question concerning whether CEA excreted by the primary tumor into the portal venous system would cross over, to any significant degree, into the biliary system and elevate gallbladder bile CEA levels. If this were the case, CEA measured in the gallbladder bile might not be indicative of the presence of metastatic tumor in the liver. It would, instead, only reflect the presence of the primary tumor.

We do not think this interpretation is correct. We believe that the CEA measured in the gallbladder bile is largely derived from CEA produced by metastatic tumor present in the liver at the time of bile aspiration, rather than from the CEA produced by the primary tumor. Although human studies have not been done, primate studies suggest that biliary excretion of CEA is low; 9% of systemic (venous) CEA is the maximum amount of CEA that can be excreted into gallbladder bile. This data suggest that for gallbladder bile CEA levels to reach 10 ng/mL or more, systemic serum levels of 100/ng/mL or more would be required.

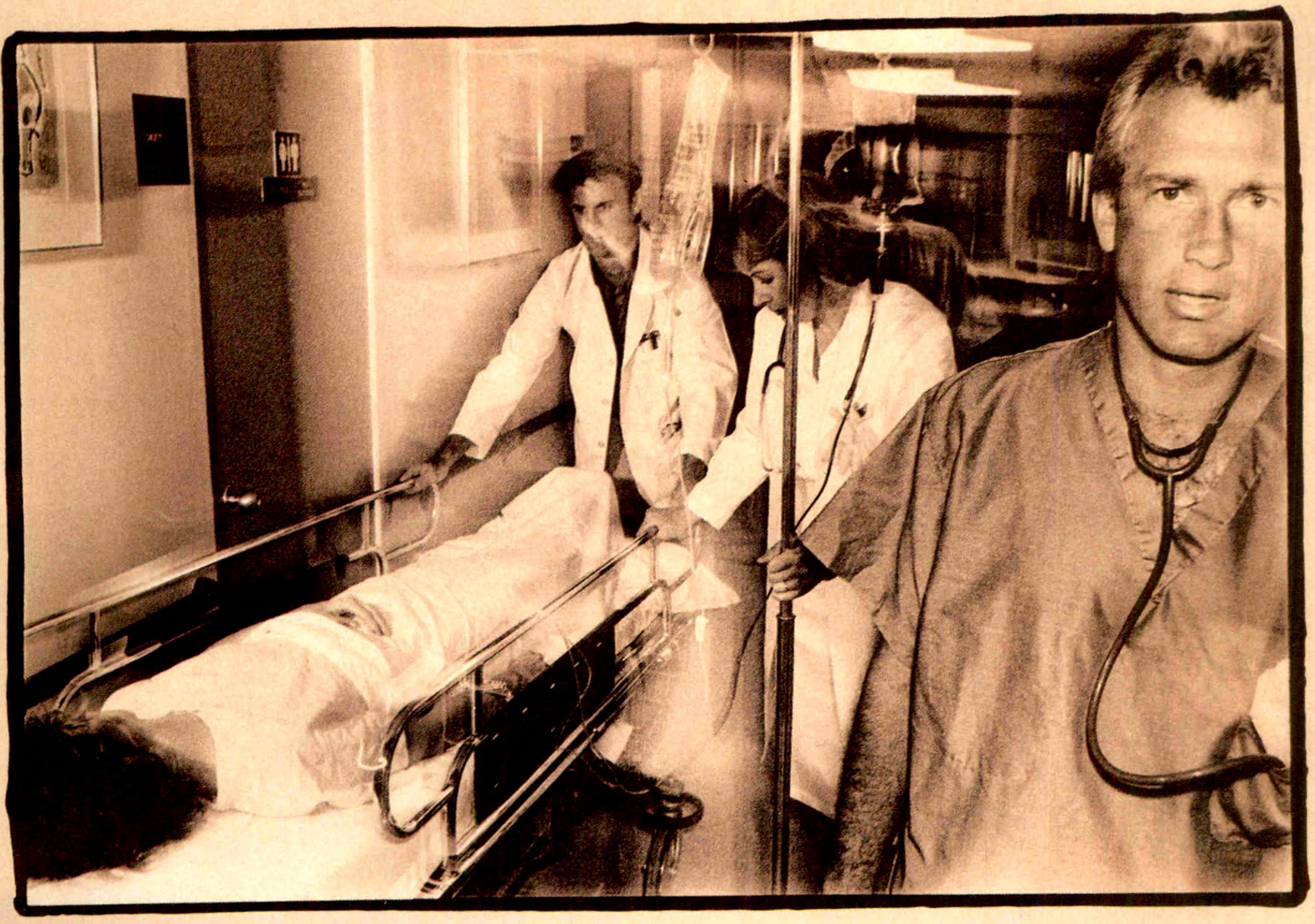
We agree with the use of intraoperative ultrasound. It can reliably detect small lesions in the hands of an experienced surgeon or radiologist. We do not anticipate that the CEA biliary assay will replace this sensitive technology; rather we believe that our assay might serve as an adjunct to other diagnostic modalities in use. We would anticipate that our assay might detect lesions as small as 1 cm^2 in surface area, which actually equates to a tumor diameter of less than 1 cm. Lesions this small often evade detection by ultrasound.

If we did find small tumors in the liver by any available method, we would try to resect them. Dr. Minton has alluded to his commendable success with resection of multiple small tumor nodules.

Dr. Minton asked a question about the source of the monoclonal antibody used in the CEA assay kits supplied by Hybritech, Inc. This particular kit is a solid-phase radioimmunoassay that uses two different murine monoclonal antibodies directed at two distinct epitopes on the carcinoembryonic antigen. The tissue-extracted CEA used to raise these monoclonal antibodies was derived from a human colon adenocarcinoma metastatic to the liver.

A note of caution is necessary for those investigators who plan to measure CEA levels in bile. There is an inhibitor within bile that interferes with the CEA assay. To eliminate this inhibitor, dilution or pretreatment of the bile is required. Attempts to measure CEA content of undiluted or untreated bile will almost always result in a false-negative result.

Were we to find an elevated biliary CEA level at the time of primary tumor resection, we would follow this patient more carefully at shorter intervals, using serial CT scans in an attempt to detect a resectable lesion as early as possible. Another option would be follow-up percutaneous aspirations of gallbladder bile to try to measure serial elevations in biliary CEA levels. Should effective portal vein chemotherapy ever be available, we would consider treatment at the time when the first biliary CEA level was found to be elevated. Radioimmunoguided surgical resection before gross visualization of tumor might also be an option should measurement of biliary CEA levels prove to be predictive of the presence of microscopic disease in the liver.



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*Efficacy for this organism in this organ system was studied in fewer than 10 infections.
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CONTRAINDICATIONS
The use of UNASYN is contraindicated in individuals with a history of hypersensitivity reactions to any of the penicillins.

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SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR HYPERSENSITIVITY REACTIONS TO MULTIPLE ALLERGENS. THERE HAVE BEEN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE THERAPY WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, UNASYN SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED.
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General: A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis. In patients treated with UNASYN the possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.
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Drug/Laboratory Test Interactions: Administration of UNASYN will result in high urine concentrations of ampicillin. High urine concentrations of ampicillin may result in false positive reactions when testing for the presence of glucose in urine using Clinitest™, Benedict's Solution or Fehling's Solution. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix™ or Testape™) be used. Following administration of ampicillin to pregnant women, a transient decrease in plasma concentration of total conjugated estriol, estriolglucuronide, conjugated estrone, and estradiol has been noted. This effect may also occur with UNASYN.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.
Pregnancy
Pregnancy Category B: Reproduction studies have been performed in mice, rats, and rabbits at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to UNASYN. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. (See—Drug/Laboratory Test Interactions.)
Labor and Delivery: Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions, and duration of contractions. However, it is not known whether the use of UNASYN in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.
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UNASYN is generally well tolerated. The following adverse reactions have been reported.
Local Adverse Reactions
Pain at IM injection site—16%
Pain at IV injection site—3%
Thrombophlebitis—3%
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The most frequently reported adverse reactions were diarrhea in 3% of the patients and rash in less than 2% of the patients.
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Adverse Laboratory Changes
Adverse laboratory changes without regard to drug relationship that were reported during clinical trials were:
Hepatic: Increased AST (SGOT), ALT (SGPT), alkaline phosphatase, and LDH.
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The following adverse reactions have been reported with ampicillin-class antibiotics and can also occur with UNASYN.
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Hematologic: In addition to the adverse laboratory changes listed above for UNASYN, agranulocytosis has been reported during therapy with penicillins. All of these reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena.

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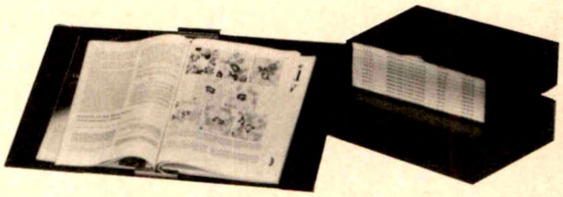

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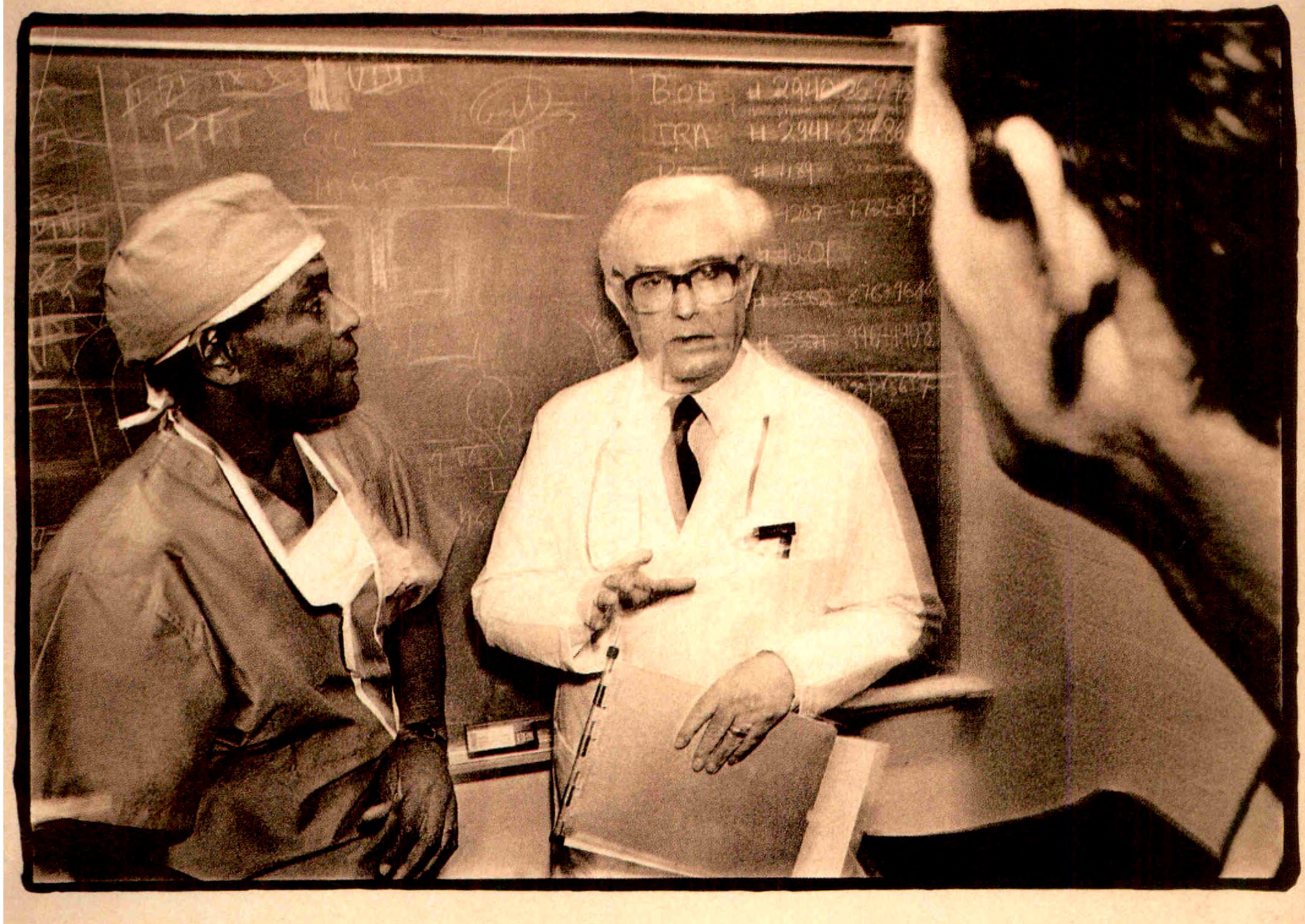

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Low-Dose Growth Hormone and Hypocaloric Nutrition Attenuate the Protein-Catabolic Response After Major Operation

ZHU-MING JIANG, M.D., GUI-ZHEN HE, SI-YUAN ZHANG, M.D., XIU-RONG WANG, NAI-FAI YANG,
YU ZHU, M.D., and DOUGLAS W. WILMORE, M.D.*

To determine the effects of low-dose recombinant human growth hormone (GH) and hypocaloric nutrition on postoperative convalescence, we performed a placebo-controlled randomized double-blind trial in 18 patients after elective gastrectomy or colectomy. The subjects received parenteral nutrition containing 20 calories/kg per day and 1 g protein/kg per day. Daily injections of drug or placebo were given during the first postoperative week. The nine control subjects lost 3.3 kg (5.9% of preoperative weight) and had a cumulative nitrogen loss of 32.6 ± 4.2 g nitrogen at eight days. The patients receiving GH lost significantly less weight (1.3 kg) and nitrogen loss was 7.1 ± 3.1 g at eight days ($p < 0.001$). Kinetic studies demonstrated that the anabolic effects of GH were associated with increased protein synthesis, and amino acid flux studies across the forearm revealed increased uptake of amino acid nitrogen in the GH-treated patients. Body compositional analysis revealed that the patients receiving GH maintained their lean body mass despite the major surgical procedure. Analysis of hand grip force showed a 10% loss of strength in the control subjects; with GH the patients maintained their grip force throughout the postoperative period. We conclude that the postoperative catabolic response can be modified with GH and hypocaloric nutrition. These metabolic and physiologic effects should now be studied in a larger number of patients to determine if this approach can reduce morbidity, mortality, and length of hospital stay for surgical patients.

From the Department of Surgery, Peking Union Medical College Hospital, Beijing, China, and the Department of Surgery, Brigham and Women's Hospital, and the Harvard Medical School, Boston Massachusetts*

THE METABOLIC RESPONSE to a major elective intra-abdominal operation is characterized by weight loss and negative nitrogen balance. Postoperative patients increase the rate of urea production and excrete urinary nitrogen in excess of intake. The cumulative nitrogen loss is generally related to the patient's weight loss,[1] which averages about 6% of preoperative body weight over 2 weeks in the patient who has an uncomplicated postoperative course.[2]

The components of the weight loss are fat, protein, and body water.[2] While adipose tissue is available for metabolic energy, the loss of body protein is of concern because there is no "storage" form of body nitrogen and body protein represents structural and functional components of the body. Loss of body protein in the short term may be of little consequence to the healthy patient undergoing an elective operation, but in the more severely ill or metabolically or physiologically compromised individual the protein–catabolic state may increase susceptibility to infection, result in poor wound healing, and prolong convalescence. Because of the relationship between protein catabolism and outcome, a variety of techniques have been proposed to alter protein breakdown and these have included nutritional support,[3] thoracic epidural anesthesia,[4] and hypothermia.[5]

We have recently investigated the effects of hypocaloric feedings combined with the administration of recombinant human growth hormone (GH) on the catabolic response. Hypocaloric feedings are usually associated with negative nitrogen balance. However when only 800 to 1200 calories were given daily along with adequate quantities of protein and GH, positive nitrogen balance was achieved.[6,7,8] As part of our ongoing effort to evaluate this approach in catabolic patients, we studied the effects of GH and hypocaloric feedings in a group of individuals undergoing gastrectomy or colectomy. GH and hypocaloric feedings greatly attenuated the loss of body weight and negative nitrogen balance that has been believed to

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Presented at the 109th Annual Meeting of the American Surgical Association, Colorado Springs, Colorado, April 10–12, 1989.

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be an indelible part of the postoperative catabolic response.

Materials and Methods

Patients

The patients were seen and evaluated in the general surgical clinic and the inpatient service of the Peking Union Medical College Hospital, Beijing, China. All individuals had a history and documented evidence of peptic ulcer disease, stable inflammatory bowel disease with stricture, or localized cancer requiring elective subtotal gastrectomy or hemicolectomy. In addition the patients satisfied the following eligibility criteria: (1) They were men between the ages of 25 and 65 years. (2) They had normal nutritional status as determined by body weight within 10% of ideal body weight, minimal recent weight loss, no evidence of nutritional deficiencies on physical examination, and normal nutritional status as determined by laboratory tests. (3) They had normal hepatic and renal function, determined by standard clinical and biochemical tests. (4) They exhibited no evidence of metastatic disease. (5) They showed no evidence of diabetes mellitus or other chronic disease and no long-term use of medications, including glucocorticoids.

The study protocol was approved by the Academic Committee of the Peking Union Medical College Hospital, which served as the institutional review board for the hospital. Written informed consent was obtained from all patients. Nineteen patients were entered into the study between December 1986 and December 1988.

Study Design

The subjects were admitted to the hospital at least four days before the date of their scheduled operative procedure. At this time they were taken to the operating theater and, using sterile technique, a triple lumen central venous catheter (Arrow, Arrow International, Reading, PA) was inserted on the right side *via* the percutaneous subclavian approach. On the morning (8:00 AM) of the third day before operation, blood was obtained for baseline studies and infusion of the parenteral nutrient solution was initiated (10:00 AM).

The nutrient solution contained 20 nonprotein calories/kg body weight per day with one half of the calories provided by carbohydrate and the remainder provided by fat emulsion (20% Intralipid, KabiVitrum, Sweden). Amino acids (Vamin-N, KabiVitrum, Sweden) were administered to provide 1 g protein/kg per day (150 mg nitrogen/kg per day). Vitamins (Vitalipid and Soluvit, KabiVitrum, Sweden) and trace elements (Addamel, KabiVitrum, Sweden) were added daily in fixed amounts to provide requirements; minerals were added daily in varying amounts to provide requirements and maintain normal blood levels. The carbohydrate, animo acid solution, vitamins, trace elements, and minerals were mixed in a 3-L bag in a laminar air flow hood. This mixture was infused at a constant continuous rate *via* the central lumen of the central venous catheter. The fat emulsion was infused separately over a 24-hour period *via* a second lumen. The total volume of the nutrient solution infused was approximately 2 L per day. Additional fluid volume (500 to 1000 mL) was administered by adding sterile water to the nutrient mixture to maintain adequate hydration. Constant nutrient infusion was maintained by using calibrated infusion pumps (Lifecare-3, Abbott, North Chicago, IL). No food or water was taken by mouth after this time until the eighth postoperative day.

The subjects were cared for in the Intensive Gastrointestinal Support Unit, which is a specialized two-bed area with dedicated nursing and pharmacy support to provide safe parenteral nutrition and collect and process all urine and other losses for analysis. Two days before operation body weight was measured and total body water was determined. Hand grip strength was also measured.

On the day of operation the patients received an epidural block to the T 6 to 9 level using Xylocaine (Astra, Sweden) and Dicaine (Beijing Pharmaceutical Co., Beijing, China) supplemented with an intravenous narcotic (meperidine) and an antihistamine (Phenergan; Wyeth Labs, Philadelphia, PA). The anesthesia was administered by a senior anesthesiologist and the operation was performed by the same team and same primary surgeon. One unit of blood was administered to each patient during the procedure. After the operation the epidural catheter was removed and the block was allowed to dissipate; narcotic was administered as required. The patient was moved back to the Unit and all urine and nasogastric losses were collected. The parenteral nutrition was administered at the same rate throughout the operative procedure. All patients received two days of perioperative prophylactic antibiotics.

On the first postoperative day the patients received an intramuscular injection of either recombinant human growth hormone (GH, Somotonorm, Kabi-peptide, Sweden) 0.15 IU/kg per day (0.06 mg/kg per day) or placebo. The patients were randomized to control or study groups by a senior laboratory staff member who drew a card from an envelope that indicated a code letter. The code letter was matched with a set of seven vials that were assigned to the patient. Each set of seven vials contained either GH or carrier substance, but the contents of the vials were unknown to the physicians, nurses, and laboratory staff. The injectate was prepared from a new vial of the set each morning and the injection was given at 7:00 AM throughout the seven postoperative days.

The nasogastric tube was removed on the second or

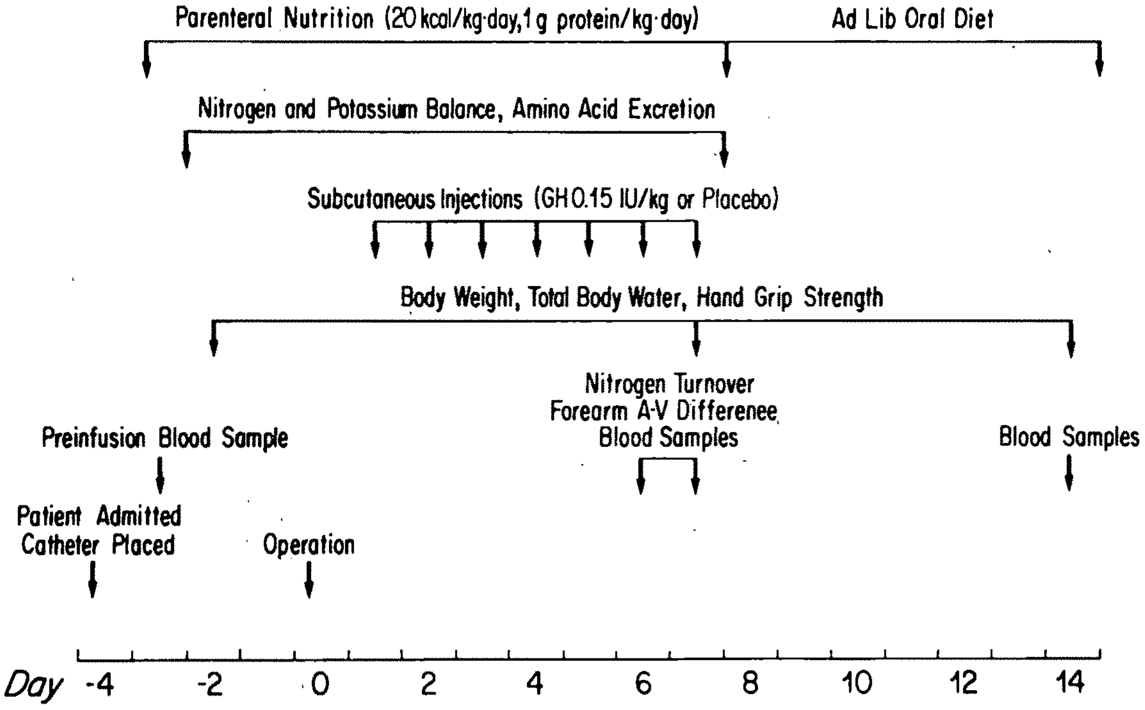
Parenteral Nutrition (20 kcal/kg·day, 1 g protein/kg·day)
Ad Lib Oral Diet
Nitrogen and Potassium Balance, Amino Acid Excretion
Subcutaneous Injections (GH 0.15 IU/kg or Placebo)
Body Weight, Total Body Water, Hand Grip Strength
Nitrogen Turnover
Forearm A-V Differenee
Blood Samples
Preinfusion Blood Sample
Blood Samples
Patient Admitted
Catheter Placed
Operation
Day -4 -2 0 2 4 6 8 10 12 14

FIG 1. Outline of study plan.

third postoperative day but the patients were not allowed to eat until the eighth post operative day, at which time the parenteral nutrition was discontinued and *ad lib* food intake was initiated.

On the morning of the sixth postoperative day, an infusion containing N15 glycine was started (Institute of Chemical Industry of Shanghai, enrichment > 95% APE). A primed constant infusion was given through a separate lumen of the central venous catheter and continued for 48 hours. The priming dose was 0.04 mg N15/kg infused over 15 minutes followed by a constant infusion of 0.016 mg N15/kg per hour. The infused volume was approximately 10 mL/hour and the infusion was given by a volumetric pump (Imed 965 micro-volume pump, Imed Inc, San Diego, CA). On the seventh postoperative day, urine samples were collected every four hours for the next 24 hours and stored for subsequent analysis.

On the morning of the seventh postoperative day while the parenteral nutrients were infusing, amino acid exchange across the forearm was measured. First a catheter was inserted in a dorsal hand vein and the hand was warmed with a heating pad to arterialize the venous blood.[9] A catheter was also placed in the basilic vein of the contralateral arm in retrograde manner to obtain samples draining the forearm muscle bed. After at least 15 minutes of rest, two consecutive blood samples were simultaneously drawn from both catheters. The sampling catheters were removed after obtaining the second set of blood samples.

On the seventh and 14th postoperative days, blood was obtained for blood chemical determination, and body weight, total body water, and grip strength in both hands were measured using a hand dynamometer (Asimow Engineering Co., Los Angeles, CA). The protocol is summarized in Figure 1.

Sample Analysis

All urine and nasogastric tube losses were analyzed for nitrogen, potassium, sodium, creatinine, and 3-methylhistidine using previously described techniques.[10] The nitrogen content in each nutrient bag was also determined, and this value was multiplied by the infused volume to determine nitrogen intake. Blood chemical concentrations were measured using a standard hospital autoanalyzer (Encore Autoanalyzer, Baker Co., Allentown, PA). Plasma, whole blood, and urine were prepared as previously described[10] and amino acid concentrations were determined using a Beckman 119 CL amino acid analyzer using physiologic runs with internal standards. Blood hormone concentrations were analyzed using radioimmunoassay techniques.[7]

The N15 enrichment of urinary urea was determined using previously described methods.[7] The enrichment of urinary urea and ammonia was determined after distillation of the sample; analysis of the ammonia produced was measured using an isotope ratio mass spectrophotometer housed at the Atomic Energy Research Institute of Beijing (model MAT-251, Finnigan Corp., Cincinnati,

TABLE 1. *Characteristics of Patients and Some Admitting Laboratory Values (mean ± SEM)*

Characteristics/Values	Control	GH
n	9	9
Age (years)	54 ± 4	41 ± 4*
Weight (kg)	56.8 ± 2.1	58.6 ± 2.3
% predisease weight	96.3 ± 1.2	97.9 ± 2.3
Height (cm)	166 ± 2	169 ± 2
Diagnosis		
Duodenal orgastric ulcer	2	5
Gastric cancer	5	3
Colonic cancer	1	1
Crohn's disease	1	0
Blood pressure (mmHg)	119 ± 6	116 ± 4
	76 ± 2	77 ± 2
Hemoglobin (g/dL)	13.2 ± 0.8	13.9 ± 0.9
White blood count (cells/cmm)	8411 ± 801	7298 ± 548
Platelet count (#/cmm)	225,200 ± 34,500	203,300 ± 33,000
Lymphocyte count (cells/cmm)	2166 ± 252	2176 ± 206

* $p < 0.05$ when compared to control by nonpaired t test.

OH). Turnover, synthesis, and breakdown were determined by standard calculations.[11]

Total body water was determined by the intravenous administration of a known quantity (40mL) of deuterium oxide. After three hours of equilibration, plasma samples were obtained, the water purified, and the deuterium concentration measured by the falling drop method.[12,13]

Calculations and Statistical Analysis

Balance was calculated as the difference between intake and measured losses in the urine and from the nasogastric tube. Because the patients received intravenous nutrition, there was minimal stool loss and this was not included in the analysis.

The arterial-venous (A-V) difference of amino acids across the forearm was determined by subtraction of each value in the venous sample from its respective arterial sample set. The mean of the two sample sets was then taken as the A-V difference. Amino acids were summed to determine quantity of essential, nonessential, and branched-chain amino acids involved in the exchange. Total amino acid nitrogen was calculated by multiplying the value for each amino acid by the number of nitrogens in a respective amino acid and summing these values.

Total body water was determined using dilutional techniques.[14] Lean body mass and fat mass were determined from body weight and total body water using described methods.[14]

After 13 patients completed the study, the code that determined what the patients received was revealed by a physician not providing primary care. The data were analyzed and the decision made to continue the study to include approximately 20 patients or proceed until the end of December 1988. The code was revealed for all investigators in 1989 after all analysis had been performed.

Statistical calculations were performed on computer (IBM 1040 [Armonk, NY] and Macintosh S.E. [Apple Computers, Cupertino, CA]) using standard statistical software (Minitab, Copyright 1986, Pennsylvania State University and Statgraphics, State College, PA). Differences were tested by two-tailed unpaired t test or paired t test, when appropriate. Hand grip strength differences were compared using the Mann-Whitney test. The effect of treatment and time on grip strength was also assessed using multiple regression. Significance was accepted at the $p < 0.05$ level.

Results

Patient Groups

Individuals who met the study criteria were randomly selected for entry into the control and GH-treated groups. Nineteen patients satisfied this criteria and were entered into the study. One individual, subject 5 (control), developed bronchopneumonia on the first postoperative day and was dropped from the study on the morning of the second postoperative day. Thus 18 patients completed the study; nine were entered into the control arm and the remaining nine received GH. The patients were well matched in terms of weight, ideal weight and height (Table 1). There was an age difference, however, with the GH group being slightly but statistically younger than controls (41 ± 4 years *vs.* 54 ± 4 years, $p < 0.05$). Other clinical measurements and preoperative studies were comparable (also see Table 9 for other preoperative tests).

Operation and Postoperative Course

The operations were performed without complications in all patients using the same operative team and a senior anesthesiologist. Epidural anesthesia was used in all patients and the level of anesthesia did not rise higher than the sixth thoracic vertebrae. Supplemental intravenous anesthesia was also administered and the quantities used were comparable in the two groups (Table 2). There were 7 subtotal gastrectomies (> 70% of the stomach removed)

TABLE 2. *Description of the Operation in the Two Groups of Patients (mean ± SEM)*

	Control	GH
Duration (hours)	2.6 ± 0.1	2.6 ± 0.1
Blood loss (mL)	160 ± 40	170 ± 20
Duration of epidural (hours)	3.2 ± 0.1	3.1 ± 0.1
Intravenous anesthetics		
Meperidine (mg)	70 ± 10	70 ± 10
Phenergan (mg)	35 ± 6	50 ± 10
Blood transfusion (mL)	400 ± 0	400 ± 0
Postoperative narcotic		
Meperidine (mg)	150 ± 24	128 ± 25

TABLE 3. *Body Temperature, Nitrogen, and Potassium Balance and Creatine Excretion (mean ± SEM)*

Control	Preoperative Day	Day of Operation	1	2	3	4	5	6	7
Temperature (°C)	36.8 ± 0.1	36.9 ± 0.2	37.4 ± 0.2	37.5 ± 0.2	37.2 ± 0.1	37.0 ± 0.1	36.5 ± 0.1	36.4 ± 0.1	36.6 ± 0.1
Nitrogen intake (mg/kg • day)	155 ± 4	159 ± 2	156 ± 2	155 ± 3	160 ± 3	159 ± 2	159 ± 2	158 ± 2	159 ± 4
Nitrogen excretion (mg/kg • day)	161 ± 9	205 ± 11	258 ± 19	218 ± 11	236 ± 15	249 ± 25	245 ± 17	229 ± 20	216 ± 16
Nitrogen balance (mg/kg • day)	−6 ± 8	−46 ± 11	−102 ± 19	−63 ± 10	−75 ± 15	−90 ± 25	−86 ± 17	−70 ± 20	−57 ± 14
Potassium intake (mEq/day)	37 ± 8	22 ± 3	25 ± 4	31 ± 6	45 ± 7	47 ± 5	45 ± 7	44 ± 8	45 ± 6
Potassium excretion (mEq/day)	22 ± 4	46 ± 10	70 ± 23	33 ± 5	30 ± 6	30 ± 5	34 ± 4	39 ± 4	34 ± 4
Potassium balance (mEq/day)	15 ± 6	−25 ± 8	−44 ± 20	−2 ± 7	14 ± 11	17 ± 8	11 ± 6	4 ± 7	9 ± 5
Creatinine excretion (mg/kg • day)	21 ± 2	17 ± 1	19 ± 2	22 ± 2	25 ± 3	22 ± 2	18 ± 1	18 ± 1	20 ± 1
Growth Hormone									
Temperature (°C)	36.6 ± 0.1	37.1 ± 0.3	37.4 ± 0.1	37.5 ± 0.1	37.0 ± 0.2	36.7 ± 0.1	36.7 ± 0.1	36.8 ± 0.2	36.7 ± 0.2
Nitrogen intake (mg/kg • day)	154 ± 1	154 ± 1	150 ± 3	154 ± 2	155 ± 2	152 ± 2‡	154 ± 2	158 ± 2	158 ± 2
Nitrogen excretion (mg/kg • day)	156 ± 7	186 ± 26	226 ± 16	210 ± 18	159 ± 12†	156 ± 19†	150 ± 15‡	138 ± 9†	140 ± 5†
Nitrogen balance (mg/kg • day)	−2 ± 8	−32 ± 26	−76 ± 16	−56 ± 17	−4 ± 10†	−3 ± 19‡	4 ± 15†	19 ± 10†	17 ± 5‡
Potassium intake (mEq/day)	38 ± 7	31 ± 7	32 ± 5	44 ± 6	54 ± 8	49 ± 6	50 ± 7	51 ± 7	50 ± 6
Potassium excretion (mEq/day)	29 ± 6	59 ± 9	42 ± 5	27 ± 5	28 ± 6	33 ± 7	29 ± 6	34 ± 6	32 ± 6
Potassium balance (mEq/day)	9 ± 3	−28 ± 9	−10 ± 3	17 ± 4*	26 ± 6	16 ± 5	21 ± 5	17 ± 4	18 ± 5
Creatinine excretion (mg/kg • day)	20 ± 1	21 ± 2	24 ± 2	24 ± 2	21 ± 2	17 ± 2	19 ± 2	18 ± 2	21 ± 1

* $p < 0.05$, †$p < 0.01$, ‡$p < 0.001$ compared by nonpaired t test with controls.

and 2 hemicolectomies performed in the control subjects, and 8 subtotal gastrectomies and 1 hemicolectomy performed in the GH group. The operative time averaged 2.6 hours and the estimated blood loss was comparable in both groups. All subjects received 400 mL of whole blood during the operation.

The epidural anesthetic was allowed to dissipate shortly after the operation and the subjects received narcotics as indicated in the postoperative period. The dosage of meperidine administered was comparable in the two groups (Table 2).

There were no complications in the subjects who completed the study. Vital signs were comparable throughout the period of hospitalization and mean body temperature did not vary between groups (Table 3). All patients had nasogastric tubes inserted in the perioperative period and these were removed in all individuals between the second and third postoperative day.

Nutrient Intake, Excretion, and Balance

The subjects received their nutrient prescription without difficulty throughout the perioperative period, and there was comparable intravenous intake of fluid, calories, and nitrogen in both groups during the seven postoperative days (Table 3).

In the control group, nitrogen excretion exceeded intake on the day of operation and the succeeding seven postoperative days (Table 3), and the subjects were consistently in negative nitrogen balance (Fig. 2). In the patients receiving GH, negative nitrogen balance occurred on the day of operation and on the first two postoperative days. Thus this early metabolic response was similar to controls. On the third postoperative day, however, these subjects excreted significantly less urinary nitrogen then the control subjects. During the last four days of the balance study, nitrogen balance approached equilibrium and became positive toward the end of the first postoperative week. Potassium excretion tended to follow nitrogen balance, but balance became slightly positive in both groups earlier in the postoperative course (Fig. 2). Creatinine excretion was comparable in both groups of patients (Table 3).

Calculation of cumulative balance demonstrated differences in nitrogen balance between control and GH-treated groups despite comparable nitrogen intake (Table

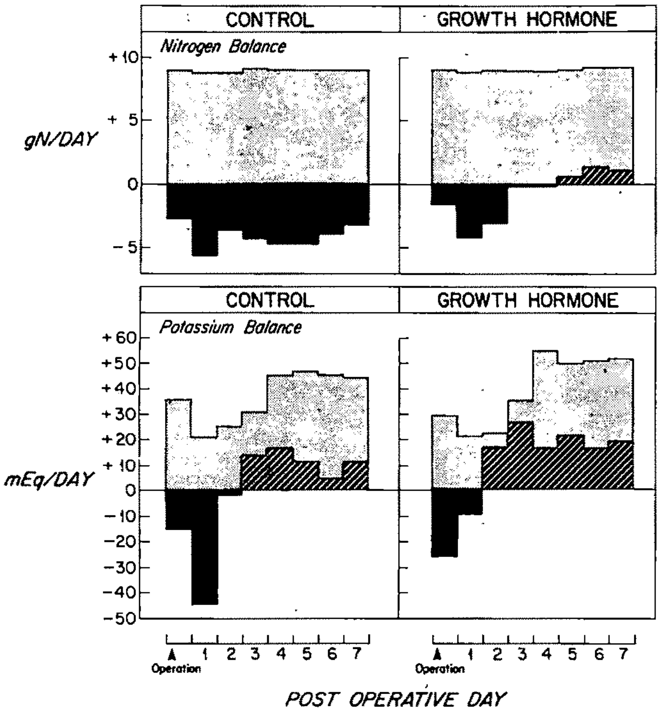

FIG. 2. Mean nitrogen and potassium balance for control and GH-treated patients. The upper line represents the quantity of the substances infused, while the black area shows negative balance and the shaded area shows positive balance.

4, Fig. 3). Potassium tended to follow this same pattern. Creatinine excretion, which reflects adequacy of urine collection, was comparable in both groups.

Nitrogen Kinetics and Amino Acid Studies

Changes in nitrogen balance can occur because of increased protein synthesis, decreased protein breakdown, or a combination of these two factors. Nitrogen turnover, calculated from the N15 enrichment of urinary urea nitrogen, tended to be greater in the GH-treated subjects (NS, Table 5).

However, the administration of GH was associated with a marked increase in nitrogen synthesis (2.19 ± 0.30 *vs.* 3.65 ± 0.47 g nitrogen/kg per day, $p < 0.05$). The rate of protein breakdown tended to increase in the GH subjects but this did not reach statistical significance.

TABLE 4. *Cumulative 8-Day Intake, Excretion, and Balance (mean ± SEM)*

	Control	GH
Nitrogen intake (g/8 days)	71.9 ± 2.8	72.3 ± 2.8
Nitrogen balance (g/8 days)	−32.6 ± 4.2	−7.1 ± 3.12†
Potassium intake (mEq/8 days)	303 ± 40	362 ± 42
Potassium balance (mEq/8 days)	−12 ± 37	+77 ± 22*
Creatinine excretion (g/8 days)	9.1 ± 0.5	9.7 ± 0.7

* $p = 0.06$, †$p < 0.001$ when compared to control by nonpaired t test.

Excretion of 3-methylhistidine, a marker of myofibrillar protein breakdown, rose from preoperative values of 4.4 ± 0.7 and 3.6 ± 0.3 μmol/kg per day in the control and GH subjects, respectively (NS), to 7.26 ± 1.01 and 4.4 ± 0.3 when assessed on postoperative day 7 ($p < 0.05$).

Before the initiation of parenteral nutrition, plasma vernous amino concentrations were in the normal range and there was no difference between groups. With amino acid infusion, these levels tended to rise slightly but not significantly (Table 6). The increase in plasma venous

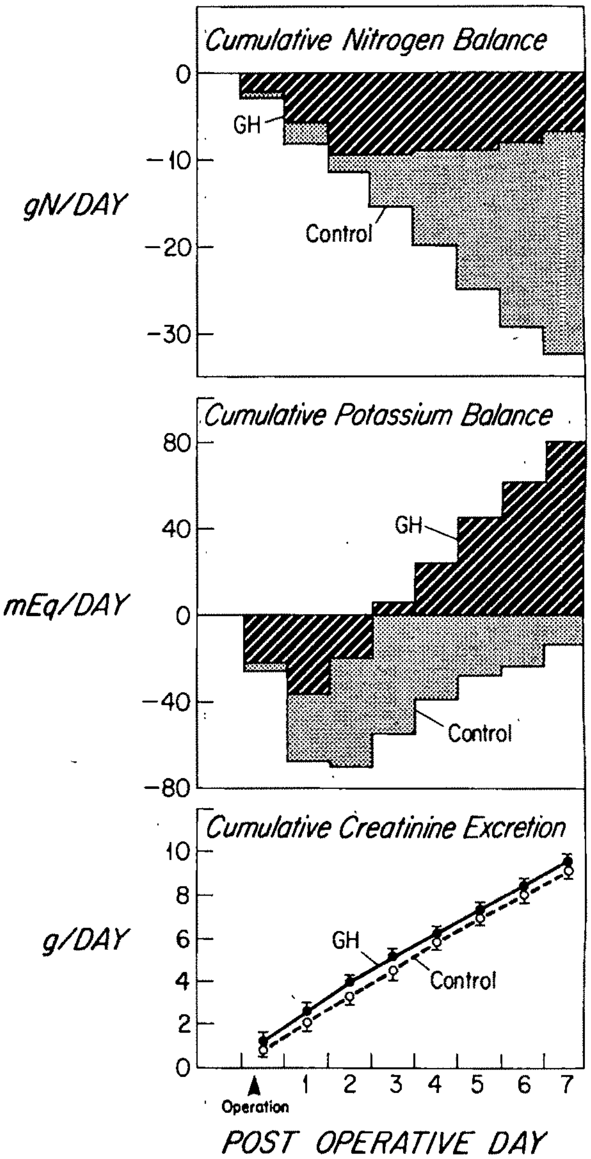

FIG. 3. The cumulative nitrogen balance was significantly different between groups from postoperative days 3 to 7. Potassium balance tended to follow nitrogen balance. Creatinine excretion was similar in both groups of patients, confirming the adequacy of urinary collection.

TABLE 5. *The Effect of GH on Nitrogen Balance and Nitrogen Kinetics Measured on Day 7 (mean ± SEM)*

	Control	GH
n	9	9
Nitrogen intake (g/kg • day)	0.16 ± 0.01	0.16 ± 0.01
Nitrogen excretion (g/kg • day)	0.22 ± 0.02	0.14 ± 0.01‡
Protein turnover (g/kg • day)	3.49 ± 0.32	4.55 ± 0.45*
Protein synthesis (g/kg • day)	2.19 ± 0.30	3.65 ± 0.47†
Protein breakdown (g/kg • day)	2.61 ± 0.30	3.55 ± 0.45*
3-methylhistidine excretion (μmoles/kg • day)	7.26 ± 1.01	4.44 ± 0.34†

* p = 0.1, †p < 0.05, ‡p < 0.01 when compared to control group.

amino acid concentration was similar in control and GH-treated subjects.

Forearm amino acid difference, measured on postoperative day 7 while the parenteral nutrients were being infused, was markedly different between groups (Fig. 4). There was continued release of amino acids from the forearm in the control subjects, while there was marked amino acid uptake in the GH-treated patients (A-V difference for total amino acid nitrogen was −398 ± 158 *vs.* +165 ± 61 μmoles/L, $p < 0.01$ with both values significantly different from zero). These alterations appeared to be due to selective changes in the release or uptake of specific amino acids, such as the branched-chain amino acids and glutamine (Table 6).

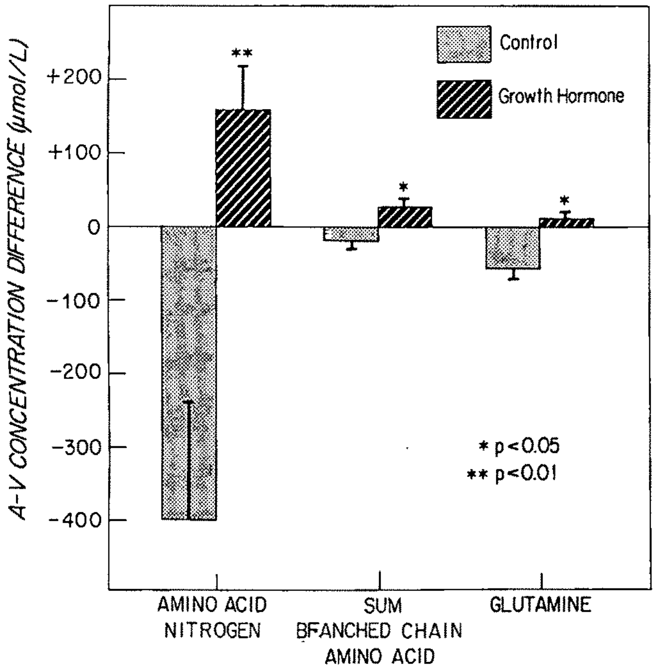

FIG. 4. The forearm of the control subjects was releasing amino acids, as shown by the negative A-V difference. In contrast, the forearm of the treated subjects' extracted amino acids. This in part could be explained by the difference between uptake and release of the branched-chain amino acids and glutamine.

Studies of Body Composition and Grip Strength

After operation, the control patients lost weight from 56.4 ± 1.9 kg to 53.2 ± 1.9 kg by the seventh postoperative day. In contrast the GH-treated patients lost weight from 58.6 ± 2.2 kg to 57.3 ± 2.3 kg (delta weight loss in controls 3.2 ± 0.3 kg *vs.* 1.3 ± 0.2 kg with GH, $p < 0.001$). Body weight tended to stabilize after the intravenous nutrition was discontinued on the morning of the eight postoperative day and *ad lib* dietary intake was started. Weight on the 14th postoperative day was 53.1 ± 2 kg for controls and 57.3 ± 2.1 kg for the study group ($p < 0.01$ for the weight change between groups when compared to preoperative values).

Total body water determinations were carried out in 15 of the 18 subjects. Before operation, total body water was approximately 35 L or roughly 60% of body weight (Table 7). While this is normal for the Chinese population,

TABLE 6. *Venous Plasma Amino Acid Concentrations Before and After Operation and Amino Acid Arterial-Venous Differences on Postoperative Day 7 (μmoles/L, mean ± SEM)*

	Control	GH
Before Infusion (3 days before operation)		
SUM essential amino acids	964 ± 82	915 ± 66
SUM BCAA	416 ± 44	415 ± 40
phenylalanine	70 ± 7	74 ± 9
SUM nonessential amino acids	2164 ± 221	1929 ± 55
alanine	351 ± 52	272 ± 26
glutamine	638 ± 56	572 ± 24
SUM amino acids nitrogen	4593 ± 432	4214 ± 161
Postoperative Day 7 (during IV infusion)		
Venous plasma concentration		
SUM essential amino acids	1046 ± 175	1125 ± 96
SUM BCAA	631 ± 55	514 ± 42
phenylalanine	105 ± 10	116 ± 13
SUM nonessential amino acids	2182 ± 140	1947 ± 107
alanine	242 ± 18	230 ± 20
glutamine	591 ± 57	528 ± 17
SUM amino acids nitrogen	4747 ± 320	4356 ± 268
A–V Difference		
SUM essential amino acids	−48 ± 40	+29 ± 27
SUM BCAA	−20 ± 16	+26 ± 12*
phenylalanine	−3 ± 6	+5 ± 5
SUM nonessential amino acids	−243 ± 77	+74 ± 50†
alanine	−24 ± 16	−3 ± 7
glutamine	−56 ± 22	+8 ± 11*
SUM amino acids nitrogen	−398 ± 158	+165 ± 61†

* p < 0.05, †p < 0.01 when compared to control by nonpaired t test. 0 = Essential amino acids contain: Val, Leu, Ile, Try, Phe Lys, Thr, and Met. 0 = Nonessential amino acids contain: Gln, Ala, Glu, Tyr, Glu, Pro, Ser, Arg, Orn, Asn, Asp, Tau, Cit, Cys, and His. − indicates release and + indicates uptake.

TABLE 7. *Changes in Body Weight and Body Water After Operation (mean ± SEM)*

	Control	GH
n	7	8
Body weight (kg)*		
preoperative	55.4 ± 1.9	57.6 ± 2.3
Day 7	52.3 ± 1.9	56.2 ± 2.3
Difference	−3.1 ± 0.4	−1.3 ± 0.2‡
Day 14	52.1 ± 2.1	56.6 ± 2.3
Difference	−3.3 ± 0.7	−1.0 ± 0.4‡
Total body water (L)		
preoperative	36.5 ± 1.4	33.7 ± 0.9
Day 7	34.1 ± 1.4	34.9 ± 0.9
Difference	−2.4 ± 0.7	+1.2 ± 0.3§
Day 14	34.5 ± 1.3	33.6 ± 0.8
Difference	−2.0 ± 1.1	−0.0 ± 0.5
Body water (mL/kg)		
preoperative	662 ± 29	589 ± 17
Day 7	657 ± 36	624 ± 15
Difference	−5 ± 17	+36 ± 6†
Day 14	666 ± 32	599 ± 16
Difference	+3 ± 17	+10 ± 6

* Listed only for those patients who had total body water measurements.

† $p < 0.05$, ‡$p < 0.01$, §$p < 0.001$ when compared to nonpaired t test with controls.

this degree of body hydration is greater than reported for individuals from Western societies. This difference reflects the increase in body fat found in Western individuals.

After operation, total body water decreased 2.4 L in the controls by the seventh postoperative day and tended to stabilize at this level throughout the next week. In contrast, the GH-treated patients maintained or increased their body water over the first postoperative week ($p < 0.001$ when compared to controls). With discontinuation of the hormone, total body water then tended to return to normal during the second postoperative week.

Calculation of body composition from this data uses standard equations that assume a normal degree of hydration of the lean body mass and do not account for expansion of the extracellular fluid compartment. Previous studies in normals and patients treated with GH show that some degree of fluid retention occurs with this treatment and that this cannot be totally accounted for by nitrogen retention.[8] Because this fluid is rapidly lost after termination of the therapy, the assumptions associated with the calculation of body composition are more appropriate for the 14th postoperative day when excess fluid has been excreted. These calculations demonstrate that the 6% loss in body weight that occurs in the control group is associated with a decrease in total body water of 2 L, a loss of lean body mass of 2.8 ± 1.46 kg (5.3% ± 2.9% of lean body mass), and a loss of 0.49 ± 1.30 kg (approximately 11%) of body fat (Table 7, Fig. 5). In contrast, the GH-treated patients lost 1.7% of body weight, essentially maintained body water and lean body mass (46 ± 1.3 kg before operation *vs.* 46 ± 1.1 kg on day 14), and lost 8.5% ± 0.4% (0.95 ± 0.46 kg) of body fat. These studies support the nitrogen balance measurements and amino acid flux studies that demonstrate that the lean body mass was preserved with this therapeutic approach. From the body compositional standpoint, the GH-treated patients had undergone a major elective operation and nearly maintained their preoperative body composition.

Hand grip strength was measured in 9 of the 18 subjects in an effort to access the functional response to this therapy. Hand grip strength fell with time in the control group (Table 8). In contrast the response in the GH-treated subjects was significantly different than controls ($p < 0.01$ for treatment effects using multiple regression analysis techniques); grip strength tended to increased with GH and was undistinguishable from the preoperative value with GH treatment at both postoperative days 7 and 14 (Fig. 6).

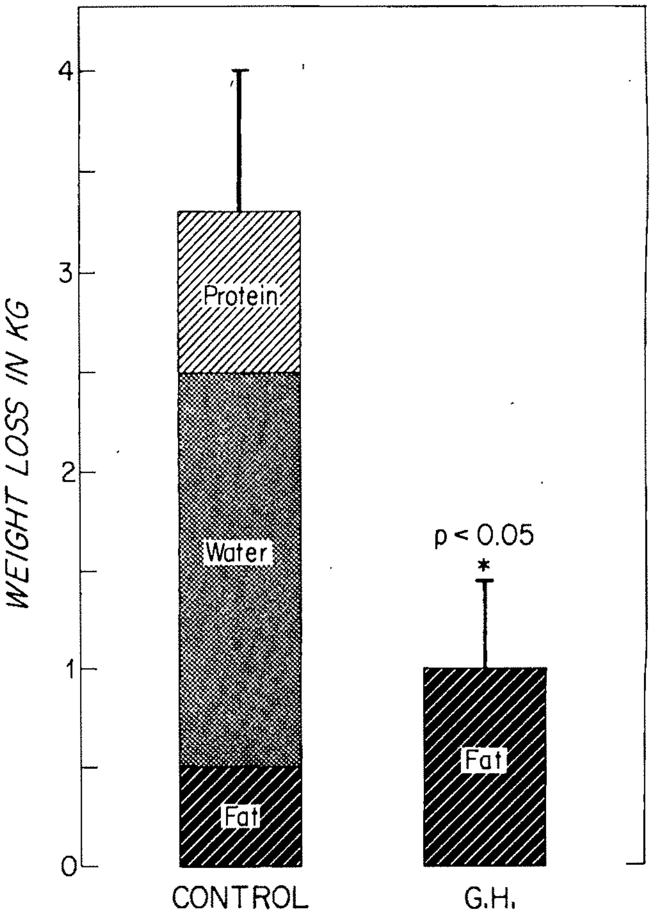

FIG. 5. The components of weight loss in controls and GH-treated patients following operation. The controls lost 490 g fat, 2 L water, and 800 g hydrated protein. In the contrast the GH-treated group only lost 950 g fat.

TABLE 8. *Hand Grip Strength Before and After Operation (kg force, mean ± SEM)*

Hand/Day	Control (n = 5)	GH (n = 4)
Right hand		
preoperative	38.2 ± 4.1	45.2 ± 5.2
Day 7	34.6 ± 4.6	46.3 ± 4.8
(change from preoperative)	−3.6 ± 2.2	+1.0 ± 0.8*
Day 14	33.8 ± 4.4	46.0 ± 5.2
(change from preoperative)	−4.4 ± 2.0	+0.8 ± 1.0
Left hand		
preoperative	38.0 ± 4.5	45.5 ± 4.7
Day 7	33.6 ± 4.8	46.8 ± 4.4
(change from preoperative)	−4.4 ± 1.9	+1.3 ± 1.26†
Day 14	33.6 ± 4.3	45.1 ± 4.4
(change from preoperative)	−4.4 ± 1.7	−0.4 ± 1.1

* Change from preoperative value (▲ response = postoperative value − preoperative value) significant difference than controls $p < 0.05$ by the Mann-Whitney Test.

† $p = 0.06$.

Blood and Hormone Values

Blood chemical values did not differ between groups when measured in the preoperative period. With operation there were moderate alterations in the liver transaminase level but there were no changes between groups. Cholesterol fell with intravenous therapy. Blood glucose levels were comparable in both groups of subjects. In contrast blood urea nitrogen level fell in the GH-treated patients (Table 9).

Serum insulin and glucagon were comparable in both groups of subjects at the time points measured. Growth hormone was elevated in the treated group and there was also a significant rise in insulin-like growth factor 1 (Table 10).

Discussion

Loss of body weight occurs after a major elective intraabdominal surgical procedure. While the extent of weight loss varies depending on the age, sex, nutritional status, and postoperative nutritional support of the patient,[15] subjects closely monitored during their convalescence have lost approximately 6% of body weight by the 12th to 14th postoperative day.[2] This response is similar to that observed in our control subjects who lost 5.9% of preoperative weight by the end of the second week. The components of the weight loss were also similar to previous reported studies. Kinney[2] studied patients after similar operative procedures. The male subjects lost an average of 34 g nitrogen (range, 17 to 67 g) during the entire period of study, 267 g water per day, and 45 g fat per day. Our control subjects lost 32 g nitrogen in the first week, and averaged a loss of 143 g water per day and 35 g fat per day during the first 2 postoperative weeks. These compositional changes are within the error of the estimates

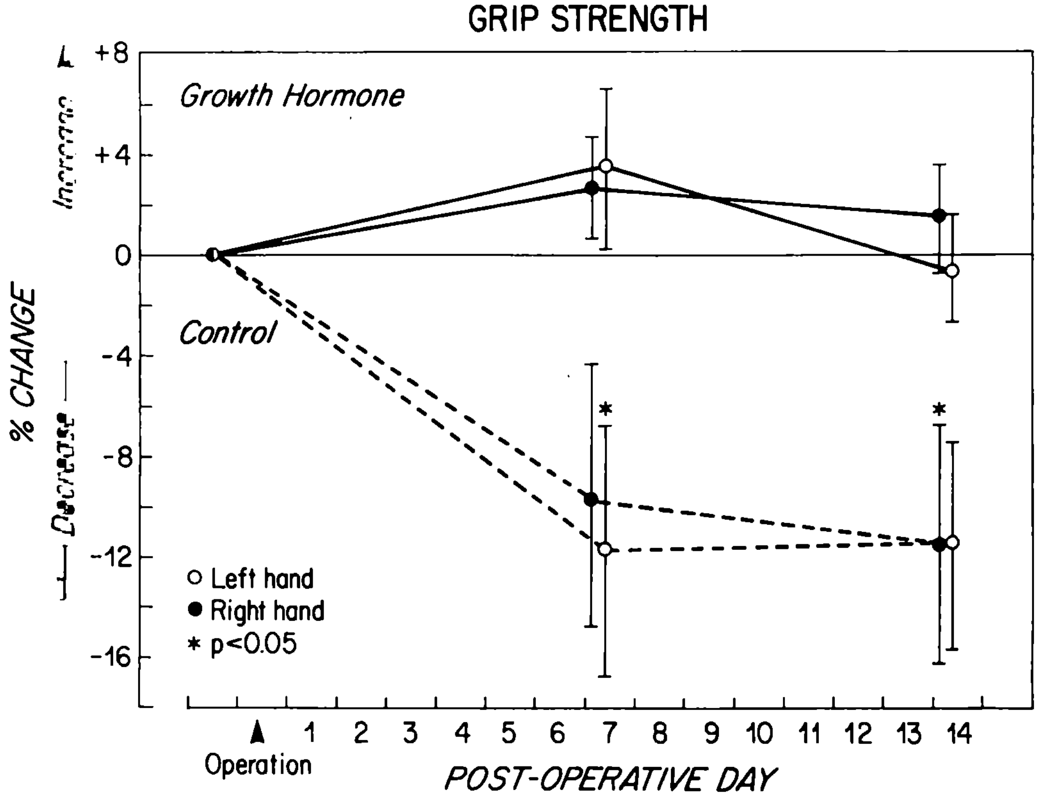

FIG. 6. After operation, the controls lost strength in both hands. However the GH-treated patients maintained grip strength.

TABLE 9. *Blood Chemical Values and Hormone Concentrations Before and After Operation (mean ± SEM)*

	Control			G.H.		
	Preoperative Day	7 Days Postoperative	14 Days Postoperative	Preoperative Day	7 Days Postoperative	14 Days Postoperative
Glucose (mg/dL)	93 ± 6	109 ± 9	95 ± 4	99 ± 6	111 ± 10	100 ± 9
Blood urea nitrogen (mg/dL)	14 ± 1	23 ± 2	18 ± 1	15 ± 1	15 ± 2*	14 ± 2
Creatinine (mg/dL)	0.9 ± 0.1	0.8 ± 0.1	0.9 ± 0.1	0.8 ± 0.1	0.7 ± 0.1	0.9 ± 0.1
Albumin (g/dL)	4.0 ± 0.1	3.7 ± 0.1	3.8 ± 0.1	3.9 ± 0.2	3.7 ± 0.2	3.9 ± 0.2
SGPT (IU/L)	22 ± 1	27 ± 5	23 ± 3	22 ± 1	27 ± 4	24 ± 3
Total bilirubin (mg/dL)	0.7 ± 0.1	0.8 ± 0.1	0.9 ± 0.1	0.6 ± 0.1	0.7 ± 0.1	0.8 ± 0.2
Cholesterol (mg/dL)	191 ± 18	164 ± 20	169 ± 17	208 ± 15	173 ± 12	192 ± 13
Triglycerides (mg/dL)	105 ± 23	107 ± 17	94 ± 12	111 ± 10	109 ± 19	115 ± 17
Total amino acid nitrogen (μmoles/L)	4981 ± 441	5011 ± 490	5225 ± 547	4214 ± 161	4356 ± 268	4045 ± 116
Insulin (mIU/L)	22.2 ± 4.6	27.1 ± 7.7	14.9 ± 2.6	14.2 ± 2.7	26.0 ± 4.4	31.8 ± 8.0
Glucagon (μg/L)	60 ± 10	56 ± 13	54 ± 12	46 ± 6	58 ± 9	59 ± 9

* $p < 0.05$ when compared to control by unpaired t test.

determined by Kinney et al.[2] and demonstrates that the fairly stereotypic responses that occur after an elective operation have not greatly changed in the past 20 years.

In contrast the patients receiving GH and hypocaloric feedings preserved their lean body mass. This was demonstrated by the nitrogen balance studies in the first week; cumulative nitrogen balance in the GH patients was − 7.1 ± 3.1 by postoperative day 7, a value that was indistinguishable from zero. The body compositional measurements demonstrated an increase in the state of hydration on day 7, and this corresponded to a decrease in body weight of 1.3 kg. Previous studies have also demonstrated that a slight increase in fluid retention occurs with GH therapy.[6,8] However these same studies demonstrate that the patients undergo a brisk diuresis with discontinuation of the hormone: after 1 week the relationship between lean tissue and body water had returned to normal. Thus the studies performed of postoperative day 14 are more appropriate for the calculation of body composition using standard equations. These calculations confirm that body water and lean body mass are unchanged in these patients; the 1 kg weight loss that did occur was attributable to loss of body fat, not protein. This is the first demonstration that a hormonal manipulation can maintain the lean body mass after a major elective intra-abdominal procedure.

TABLE 10. *The Effects of GH Administration on GH and IGF-1 Concentration (mean ± SEM)*

	Control	GH
Growth Hormone (μg/L)		
preoperative	5.5 ± 2.4	4.2 ± 1.7
Day 7	3.2 ± 1.7	65.6 ± 15.1†
IGF-1 (μg/L)		
preoperative	211 ± 16	249 ± 19
Day 7	237 ± 33	463 ± 44*

* $p < 0.05$, †$p < 0.01$ when compared to controls by nonpaired t test.

The catabolic effects of an operation are probably most evident on skeletal muscle, which represents the largest single tissue compartment of body protein. That the net catabolism of body protein is increased in the control subjects after operation is evident by the negative nitrogen balance, loss of lean body mass, increased amino acid efflux from the extremity, accelerated excretion of 3-methylhistidine (a marker of myofibular protein breakdown), an increase in the rate of protein breakdown over synthesis, and a decrease in muscle strength. With GH these alterations were all significantly reversed.

One of the most dramatic changes observed occurred with the uptake of amino acid across the forearm. This alteration in A-V difference was so apparent that it was not necessary to calculate a flux rate (the multiplication of forearm blood flow times A-V difference). This occurred because the control group continually lost amino acid from the forearm muscle bed while GH reversed this gradient, resulting in a significant decrease in venous amino acid concentration when compared to arterial concentration. Uptake of amino acid across resting skeletal muscle has not been observed after a long-term hormonal manipulation and previous reports of amino acid exchange across the extremity during the infusion of parenteral nutrition have consistently demonstrated that the skeletal muscle continues to release amino acids in spite of "adequate" nutrition.[16,17]

The measurement of nitrogen kinetics support the concept that the effects observed are related to increased protein synthesis. This is similar to previous studies in normal individuals receiving GH.[7] Although there was a trend toward increased nitrogen turnover and breakdown with GH, these alterations did not achieve statistical significance (Table 5). However other investigators have reported changes in all components of nitrogen kinetics in postoperative patients receiving GH,[18] and it is probable that the rate of movement of amino acids through many metabolic pathways is increased, a state associated with the support of tissue growth and maintenance of tissue turnover.

The trend to increase the rate of protein breakdown with GH seems inconsistent with the 3-methyl histidine excretion data, which suggests that a diminished rate of breakdown was occurring in the myofibular protein pool, represented in large part by skeletal muscle. It is probable that the rate of protein synthesis is somehow linked to the rate of protein breakdown and it may be that augmentation of skeletal muscle synthesis in postoperative patients receiving GH may dampen the accelerated rate of muscle breakdown. However one would expect this response to be reflected in the isotopic kinetic data, which demonstrated that breakdown tended to increase, not decrease. There may be several possible explanations for these results. First these techniques may not be sensitive enough to simultaneously detect the same changes. Conversely these measurements may be quantitating turnover in different pools of protein; breakdown rate may be decreasing in skeletal muscle while turnover is accelerated in other tissues, particularly abdominal organs.

Of most importance, however, is the association between improvement in protein metabolism and the increase in muscle strength. The postoperative loss of muscle strength has been carefully studied and commonly occurs after all major operations.[19] The components of this response are complex and are related in part to nutritional factors and both cardiovascular and exercise deconditioning. Our control subjects lost grip strength in both arms after operation; in contrast GH-treated individuals increased or maintained grip strength. The response to therapy as shown by the lack of change in hand grip force has not been previously observed. The initial preoperative measurements demonstrated that the GH-treated subjects tended to have a greater grip strength then control subjects (NS). It could be argued that this might account for the absolute differences observed, although there is no physiologic basis to explain why a baseline shift might explain why one group would have diminished grip strength in the postoperative period and the other group maintained grip force. Subjective influences affect this measurement, but it is difficult to understand how this could influence the results in a placebo-controlled double-blind trial. Thus we conclude that these effects are the result of GH treatment and this response is a functional manifestation of the metabolic results that have been documented in this study.

The changes in hand grip force confirm our previous observations that patients receiving GH have increased strength and activity. This may be demonstrated by increased self care, ambulation, and independence. In more seriously ill patients this may be seen by increased respiratory muscle strength and the ability to cough, breathe deeply, and to be weaned from the ventilator. If this response can be confirmed in additional studies, this type of approach may have specific advantages in accelerating postoperative recovery and shortening surgical convalescence as we appreciate it today.

Finally the metabolic response to operative stress was markedly altered with minimal patient risk. The hypocaloric nutrients represent a nutrient formulation that contains 150 to 200 g glucose and this can be infused by peripheral vein. Hyperglycemia did not occur and unexpected alterations in electrolyte or amino acid concentrations were not observed. The dose of growth hormone used was approximately 9 IU/day (about 3.3 mg/day) or approximately one third of the dose we have administered to more catabolic patients. This lower dose may account for the reduced side effects, and use of such doses also reduces cost.

This study demonstrates the direct influence that the revolution in biotechnology has had on surgical care. GH was not previously available in large quantities because the only source was the human pituitary gland. Bioengineering developed a method of hormone manufacture and this agent is now readily available. In this study in postoperative patients, GH and hypocaloric feedings markedly attenuated the catabolic effects of a major surgical procedure. This was associated with maintenance of the lean body mass at preoperative levels, attenuation of urinary nitrogen loss, uptake of amino acids across the forearm, and increase or maintenance of skeletal muscle strength. Studies are now underway to determine if these metabolic and physiologic effects can be correlated with reduced morbidity and mortality and diminished hospital stay in surgical patients.

Acknowledgments

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DISCUSSION

DR. PAUL SCHLOERB (Kansas City, Kansas): This is another landmark article from the Wilmore group—this time from Beijing. The paper presents many questions. How little growth hormone can be given to achieve this effect? Do these amounts of calories, carbohydrate, and protein represent minimum necessary quantities? What is the role of exercise? Some of the kinetic data presented in the paper would suggest that exercise might indeed play a part and influence these kinetics.

How long was the blinded status maintained? As I understand it, there is a euphoric effect from giving growth hormone. I wonder if the patients themselves may have given the secret away.

What about the side effects? Is there a depressive effect when it is stopped? Is hypersensitivity to growth hormone used in these circumstances a real consideration?

These studies were done on elective operations. It is a tribute to the surgeon that there were no complications in either the control or the experimental groups. Of course the real bottom line is the treatment of patients with complications such as sepsis and fistula. Do you have any experience, albeit anecdotal, on the treatment of patients with complications?

Finally, I would emphasize that this work has very wide spread implications for the understanding and the further supportive care of our surgical patients.

DR. BASIL A. PRUITT, JR. (Fort Sam Houston, Texas): Dr. Jiang, Dr. Wilmore, and their colleagues have presented data suggesting that it is possible to modify and, in part, abrogate the postoperative catabolic response. Even more impressive is their finding that recombinant human growth hormone, even in a hypocaloric setting, can maintain muscle strength and perhaps accelerate convalescence.

There are some puzzling and perhaps paradoxical aspects of this randomized prospective study that I hope the authors will clarify to assist us in interpreting their findings.

Although the operations performed on the study patients appear to have been generally comparable, were the metabolic rates measured and, if so, were the metabolic rates of the two groups comparable?

It is puzzling that the preintervention growth hormone levels were higher in the older patients because it is well known that growth hormone levels decrease with age. Do the authors have an explanation for that finding?

The authors note that additional fluids were added to the standard daily nutritional volume to maintain adequate hydration and it appears in Table 7 that the difference in weight change between the control and treatment groups at seven days can be entirely explained by the 3.6-L difference in total body water favoring the growth hormone group. The observed difference in BUN levels is certainly consistent with that possibility. Even at day 14, the 2.3-kg weight difference seems to be consistent with the 2-L difference in total body water; I wonder if the intake and output records of these patients confirm or refute that possibility?

The authors note a temporal dissociation between potassium and nitrogen balance. Since those balances tend to move in parallel, how do the authors explain the observed dissociation? The greater positive potassium balance is offered as a beneficial effect of the growth hormone therapy, but it is of concern to note that the growth hormone group received 19% more potassium. That in itself may account for the observed difference in potassium balance.

The authors explain the finding of increased amino acid uptake in a setting of increased protein breakdown on the basis of a differential effect of growth hormone on viscera and carcass. In this regard the timing of the forearm amino acid exchange studies vis-a-vis the daily growth hormone injection is of concern because the rapid stimulating effects of growth hormone on amino acid transport and protein synthesis are expressions of the insulinlike action of growth hormone and not manifestations of its growth-promoting action. To eliminate such a transient time-related effect, were similar studies done at other times of the day to confirm that this was a manifestation of persistent growth activity?

The authors note that body composition changes indicate that the growth hormone patients lost predominantly body fat, and certainly lipolysis is a well-known effect of growth hormone. As corroboration for the importance of that effect, do you have data showing that those patients treated with growth hormone had increased circulating levels of glycerol and free fatty acids?

I again compliment these authors on an important study that suggests that it is possible to shorten hospital stay after major surgery.

DR. JAMES MACKENZIE (New Brunswick, New Jersey): Dr. Mannick, I, too was fascinated with all of the implications of the study. I have one question. Has this study been done by the authors or others with comparison of operative and nonoperative groups? In other words, with merely infusion of the growth hormone or a placebo?

DR. STANLEY R. FRIESEN (Kansas City, Kansas): I, too, congratulate Dr. Wilmore, a former Kansas student, on this beautiful clinical investigation.

I would like to ask one question. What would he expect if he had substituted insulin or androgens as other anabolic products for growth hormone in this study?

DR. STANLEY M. LEVENSON (Bronx, New York): What is most striking to me in their findings is the maintenance of hand strength in the patients treated with growth hormone in contrast to the loss of hand strength in the patients not receiving growth hormone. Although the difference in nitrogen balance in the two groups of patients is statistically significant, from the quantitative point of view the difference represents a very small percentage of skeletal muscle mass. It would seem unlikely that the improvement in nitrogen balance due to growth hormone administration would account, *per se*, for the maintenance of hand muscle strength by the growth hormone-treated group of patients and the loss of hand strength in the control group.

I would like Dr. Wilmore to speculate about the mechanism(s) underlying the striking effect of growth hormone on the maintenance of hand strength.

DR. DOUGLAS W. WILMORE (Closing discussion): One man who usually discusses our work is Dr. George Clowes, who is not with us now. We will miss his perspective and advice on these matters.

Dr. Schloerb asked about the minimal quantities of hormone that we can give. In general, we have used growth hormone in doses of 10 mg per day. This study used doses of about 3 to 4 mg per day. If you account for the size of the individuals, this is about one half the amount that we are using in Boston.

We do not know if there would be an effect using even smaller doses, but there are other trials now in progress that are using larger doses. We would suspect that as we use larger doses, there will be additional side effects from the drug. One of the great advantages of this approach was that we can use peripheral vein infusions to deliver nutrients, and with the very low dose of growth hormone complications are not a major concern.

We administered 20 calories/kg body weight per day and those calories were divided between fat and carbohydrate. My own bias is that we can remove the fat from the nutrient solution and give 10 calories per kilogram as carbohydrate. That provides about 150 or 200 g of carbohydrate, which is the minimal amount of carbohydrate required for obligate glucose using tissues. By providing the required quantity of carbohydrate and adequate protein in this anabolic environment, we can use the patients fat stores for the additional energy and achieve anabolic effects. This type of approach should actually be initiated in the preoperative period so that we can really accelerate protein synthesis in patients undergoing an operative procedure. This may have a major impact in shortening hospitalization and reducing complications.

Patients who receive growth hormones often experience euphoria. We could not get an indication as to whether this response occurred in the postoperative patients. When I went through the patient list and asked the health care providers to name what subjects received the drug, we saw only random selection.

In contrast, however, our burn unit nurses can consistently tell me who are the patients receiving the drug in blinded trials, and this is simply because they see accelerated rates of wound healing.

In addition to the euphoria, patients may have increased strength. We have had patients paralyzed and on the ventilator for more than 40 days and on the first day they have been taken off the ventilator they get out of bed and walk 50 feet or so. That is a phenomenon that I have never seen before, and again points out the role of this particular substance on the muscle energetics and muscle dynamics.

We have used this drug on patients with complications. If it increased leg and arm muscle strength, it should increase strength in respiratory muscles. This would be a great advantage to patients who were on ventilators and could not be weaned by usual means. This evaluation is now proceeding in double-blind trials.

Dr. Pruitt, we didn't measure metabolic rates. Pretreatment concentrations of growth hormone are variable, but growth hormone really needs to be monitored frequently over a long period of time to establish stable levels.

Potassium balance was more positive in the growth hormone-treated group, but the serum levels fall with growth hormone treatment, and hence more potassium is required. Water balance in the first week generally reflected the changes described by the body compositional data, but in the second week water balance was not done when these subjects were on ad lib feedings. We did not look at fatty acid and glycerol turnover in these studies.

Dr. MacKenzie, we have done growth hormone studies in normal volunteers. This fact was advertised in Boston and many people from the weight lifting gym called to volunteer. We have given normal volunteers as little as one third of their caloric intake, adequate protein, and growth hormone and put them into positive nitrogen balance.

Dr. Friesen, we would expect that androgens would have a weak anabolic effect. That is, the steroids that the athletes are using would have some effect, and in fact, one investigator has given androgens along with growth hormones to a group of young women and had actually an additive anabolic effect from both of these agents.

Insulin would not have a similar effect unless we gave more glucose to prevent hypoglycemia. The particular advantage of this approach is that we can give nutrients by peripheral vein and have them assimilated to target tissue.

Again, Dr. Levenson, the muscle effect is very interesting. We have hypothesized that growth hormone may alter muscle energetics because we see muscle effects very shortly after we administer the drug, too rapidly to be accounted for by the protein synthetic effects and more consistent with effects on ATP generation within skeletal muscle itself. If this were so, this would be a real advantage during postoperative convalescence.

Finally, I would like to introduce Dr. Jiang, the principal investigator to the group, and again acknowledge his primary role in this investigation.

The Use of Intraoperative Echo with Doppler Color Flow Imaging to Predict Outcome After Repair of Congenital Cardiac Defects

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Surgical repair of congenital cardiac defects (CCD) has undergone a remarkable evolution in the past decade. Major defects are now often completely corrected in early infancy with continually improving rates of survival. It has become clear that the next major focus will be improvements in the long-term quality of life and this has prompted many innovations in surgical technique and approach. One advance is the use of intraoperative echo with Doppler color flow imaging (echo-DCFI) to evaluate the exactness of operative repair. Aside from anecdotal reports, very little information is available regarding the interpretation of images produced by this technology in the operating room. Furthermore there have been no studies addressing the predictive value of intraoperative echo-DCFI findings with respect to outcome for patients undergoing repair of CCD. The prospective data obtained by following the course of 273 patients receiving intraoperative echo-DCFI has been reviewed after repair of a variety of CCD (age range, 1 to 53 years; mean 5.3 years; smallest patient, 1.8 kg). Forty-seven patients (17%) had initially unacceptable results, by echo, at the completion of their repair. Eighteen of these patients (7% of entire series) had no clinical problems and the defects were discernible only by echo. Twenty-six patients with initially unacceptable results had their repairs revised in the operating room and left with an acceptable result by echo. Twenty-one patients were allowed to leave the operating room with echo-discernible defects. Follow-up of these patients demonstrated a significantly higher ($p < 0.006$) rate of reoperation (42% *vs.* 3%) and of early death (29% *vs.* 10%) for those patients whose defects were left unrepaired compared to those whose problems were corrected before leaving the operating room. Sixty-eight patients (25%) had some alteration of ventricular function (compared to their prebypass evaluation) at the completion of their repair. Regardless of whether the dysfunction was limited to the right ventricle, left ventricle, or was biventricular, patients in this group had a significantly higher incidence ($p < 0.004$) of early, but not late, death compared to patients without alteration of ventricular function (35% *vs.* 4%). Patients who left the operating room with no problems of concern by echo-DCFI had a greater than 90% likelihood of a long-term acceptable outcome compared to patients who had any problem of concern (residual defect, anatomic or technical imperfection, ventricular dysfunction, and so on) whose long-term likelihood of an acceptable outcome approached 50% ($p < 0.0125$). The results of this study demonstrate that echo-DCFI can provide useful information to surgeons at the time of repair for CCD that can be directly correlated with the quality of patient survival that can be expected.

THE MOST CRITICAL ELEMENT in achieving successful repair for congenital heart defects is the performance of technically accurate and efficient surgical reconstruction. The quality of life for each patient is unquestionably affected by the events in the operating room and it would seem that those patients who receive the best anatomic results will enjoy the best long-term outcomes. Advances in technology have increased the safety of performing major reconstructive procedures in pediatric cardiac patients so that immediate operative survival is greatly enhanced, and surgeons are now beginning to evaluate results with respect to the quality of life that patients can attain with each repair. This shift in focus has led to several changes, including increasing popularity of total anatomic correction in younger and smaller patients with various complex congenital cardiac defects.[1] Regardless of the type of operation performed, and the age of the patient at the time of correction, it is incumbent on the surgeon to provide each patient with the best results possible, given the anatomy of the lesion, to insure the best quality of survival. Towards this end, surgeons have evolved several methods to increase their efficiency, including improved methods of myocardial protection and better understanding of the usefulness of

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deep hypothermia with periods of total circulatory arrest. Methods of evaluating the success of each repair in the operating room have been less satisfactory. By using a combination of pressure measurements, oxygen saturation data, and green-dye curves, it is possible to obtain an indirect and relatively insensitive appraisal of the adequacy of a repair, but none of these methods enables the surgeon to visually judge the degree of anatomic and functional normalcy created by the repair. The recent introduction and popularization of intraoperative echo with Doppler color flow imaging (DCFI)[2–5] has provided the surgeon with a new tool for this purpose, but the implications of the findings displayed by this extremely sensitive technology are not well understood. This prospective study was designed to analyze the efficacy of intraoperative echo-DCFI in providing prognostic information regarding the quality of operative repairs for congenital cardiac defects so that information provided by this method can be better interpreted and used in the operating room.

Methods

Between March 1987 and March 1989, 273 patients undergoing median sternotomy for correction of congenital cardiac defects at the Duke Heart Center were evaluated both before and after cardiopulmonary bypass (CPB) using echo-DCFI. Diseases treated are listed by primary diagnosis in Table 1. Patients ranged in age from 1 day to 53 years (mean, 5.3 years) with 97 patients (37%) less than 1 year old and 152 patients (56%) less than 3 years old. The smallest patient weighed 1.8 kg.

Intraoperative echo-DCFI was performed using a Hewlett-Packard HP77020CF (Hewlett-Packard, Andover, MA) color flow imaging device equipped with multiple transducers. Data were collected from an epicardial transducer in 260 patients (96%), a transesophageal transducer in 4 patients (1%), and a combination of the two techniques in 9 patients (3%). The epicardial approach was selected for the majority of the patients due to their small size, which effectively eliminated the possibility of using the larger, more cumbersome transesophageal transducers. Furthermore the complex nature of many of these lesions favored the more versatile epicardial approach because it enabled the surgeon to obtain views of the anatomy from a variety of orientations, thus demonstrating each defect in exquisite detail. The techniques for placement of the transducers has been described previously.[3,6,7]

All images were analyzed "on-line" in real time and decisions were made in each case on the basis of echo-DCFI as well as any other relevant clinical observations available. All echo-DCFI data were evaluated mutually and by consensus of the attending surgeon, anesthesiologist, and cardiologist present during the procedure. These data included evaluation of the quality of the repair with respect to residual structural defects (VSD, ASD, outflow obstruction, and so on) or concerns with the adequacy of newly created flow patterns in conduits, valves, outflow patches, and so on as detectable by echo-DCFI, as well as changes in ventricular function compared to pre-CPB exams. Data from each study were entered into a data bank for later retrieval and analysis.

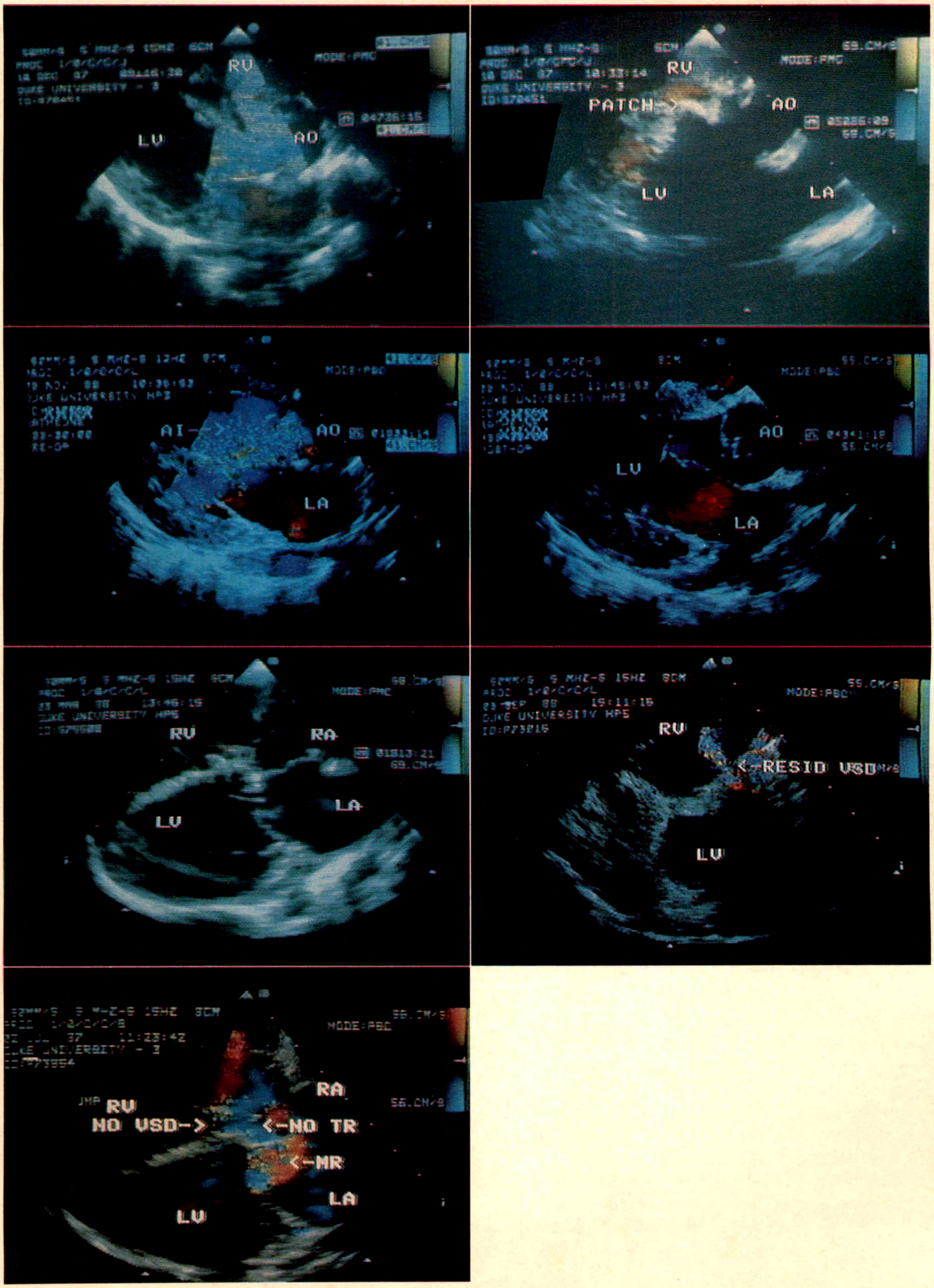
TABLE 1. *Intraoperative Echo-DCFI for Congenital Heart Repair*

Principal Diagnosis	N = 273
Tetralogy of Fallot	37
Ventricular septal defect	39
Atrial septal defect (Secundum, Primum, Sinus Venosus)	40
Atrioventricular septal defect (complete)	26
Valvular regurgitation	23
Congenital valvular aortic stenosis	15
Transposition of the great vessels	15
Univentricular heart	12
Pulmonary atresia	13
Tricuspid atresia/stenosis	9
Subvalvular aortic stenosis	9
Double outlet right ventricle	7
Aortic arch anomaly	7
Total anomalous pulmonary venous return	4
Coronary anomaly	4
Truncus arteriosus	2
Others	11

With respect to quality of repair, patients were categorized in one of two major classes: those with acceptable results (no significant residual defect) and those with "residual defects" that were believed to be of some concern. These classes were based on echo-DCFI images without regard to the patient's clinical condition. The patients with acceptable results had either "echo-perfect" repair, without any evidence of persistent anatomic disturbance, or had minimal "residual defects" that were believed to be quite insignificant given the well-known sensitivity of this technology[8–10] (Figs. 1 to 3). If the post-CPB echo displayed residual shunt flow that was associated with pronounced turbulence and suggestive of more significant leakage, or function of a repaired valve that demonstrated persistent stenosis or regurgitation of moderate degree, the repair was believed to represent one with a "residual defect of concern" (Figs. 4 and 5).

Any change in ventricular function from the pre-CPB status was also recorded. Records were kept to distinguish whether the dysfunction occurred in the right ventricle, left ventricle, or globally. Changes in chamber size and in contractile patterns were noted. Finally patients were also analyzed with respect to whether they left the operating room with any problem of concern compared to their preoperative exam and given the nature of their intended repair. All statistical analysis was provided by the standard chi square test using a Bonferroni correction factor to allow for multiple variables.

Patients have been followed carefully for quality of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FIGS. 1A and B. (A, *first row, left*) Epicardial long-axis view of a perimembranous ventricular septal defect in a 2-month-old baby with substantial turbulence from left to right shunting. (B, *first row, right*) Appearance after operative repair with patch securely in place, demonstrating no residual shunt flow characteristic of echo "perfect" results.

FIGS. 2A and B. (A, *second row, left*) Long-axis epicardial image from a 4-year-old patient with severe aortic insufficiency after attempted balloon valvuloplasty in the cath lab. (B, *second row, right*) Image obtained during diastole from the epicardial surface after aortic valve repair. There is no evidence of any residual aortic insufficiency, documenting a very acceptable result.

FIG. 3. (*Third row, left*) Postbypass epicardial image from a 7-month-old infant after repair of a complete AV canal defect. A small amount of residual ventricular septal shunting and mitral regurgitation are present. Neither of these were believed to be hemodynamically significant and this constitutes an acceptable result.

FIG. 4. (*Third row, right*) Residual ventricular septal defect after "successful" intracardiac baffling for a patient with double outlet right ventricle. This is considered a "residual defect of concern," and thus a suboptimal result.

FIG. 5. (*Fourth row*) Residual mitral insufficiency after repair of complete AV canal defect in a 6-month-old infant who had been previously banded. Of note there is no residual ventricular septal defect in this patient, but the turbulence at the level of the mitral valve classifies this degree of insufficiency as unacceptable.

outcome. To maintain the most objective appraisal of outcome, definitive markers were chosen: reoperation for the same problem at any time, or death. Death was classified as "surgical" (within 30 days of surgery), or "late" (after 30 days). Patients were recorded as having died, even if they died from causes unrelated to their cardiac disease and regardless of whether they had been discharged from the hospital. Follow-up has been performed for a range of 1 day to 2.1 years (mean, 1.02 ± 0.58 years). The data base is ongoing and reflects all current information available about each patient. No patients have been lost to follow-up.

Results

There was no difficulty encountered in determining which patients presented postrepair defects or ventricular function problems of concern. The implications of these findings were examined by interrogating the data base.

Residual Echo Findings of Concern

Forty-seven patients (17%) presented echo findings that were cause for concern after initial repair. In 36 of these patients, an attempt at revision was performed, and in 11 patients, no further surgery was performed. It is interesting to note that in the group of patients in whom revision was attempted, the data that led to the decision to reconstruct a portion of the repair was provided solely by echo-DCFI in 21 patients (58%) and from a combination of echo findings confirmed by clinical suspicions in 15 patients (42%) (Table 2). Eighteen (86%) of those patients whose repair was revised exclusively on the basis of echo information left the OR with an acceptable result by echo-DCFI. These 18 patients represent 7% of the entire series. Twenty-four patients in the overall series left the operating room with persistent "residual defects" as defined by echo-DCFI. Table 3 displays the impact of residual defects disclosed by echo-DCFI as they relate to the incidence of reoperation or death during the postoperative period. Table 4 separates the group of 47 patients who had initially unacceptable repairs (by echo-DCFI) into two groups: those who left the operating room with an acceptable revision (26 patients) and those who left without revision (21 patients). This table documents the long-term outcome, depending on how these relatively similar problems were dealt with before leaving the operating room.

Table 5 displays similar outcome data for the patients in this study in terms of changes in ventricular function in the immediate post-CPB period. Table 6 looks at outcome based on the presence of any post-CPB echo-DCFI problem of concern (*e.g.*, residual defects, ventricular dysfunction, disturbing anatomic or physiologic features, and so on).

Discussion

The data from this study clearly demonstrate the value of intraoperative echo-DCFI during the repair of congenital heart defects. Eighteen patients in this series (7%) had immediate successful revision of their procedure based entirely on the information displayed by the color flow images. None of these patients demonstrated any suspicious clinical problems, and without routine echo-DCFI evaluation they would have likely left the operating room with a suboptimal repair. These findings alone stimulate several intriguing questions: Would these problems have been identifiable by the other available methods for eval-

TABLE 2. *Intraoperative Echo-DCFI for Congenital Heart Repair: Reason for Revision in 36 (13%) Patients*

	Redone	Acceptable Result
Clinical problem (echo-DCFI confirms)	15	8
Echo-DCFI alone	21	18
Total	36	26

TABLE 3. *Intraoperative Echo-DCFI for Congenital Heart Repair: Outcome Relating to Final Echo Results in 273 Patients*

Residual Defect (Echo)	N	Acceptable Outcome	Reoperated	Surgical Death	Later Death
No residual defect	247 (90%)*	210 (85%)	8 (3%)	24 (10%)	5 (2%)
Residual defect	24 (9%)*	5 (21%)†	10 (42%)†	7 (29%)†	2 (8%)
Cannot evaluate	2 (1%)*	1 (50%)	0	1 (50%)	0

* Of entire series.

† $p < 0.006$ by chi square (compared to no residual defect).

uating results (*e.g.*, dye curves, pressure measurements, or oxymetry data)? How significant were these discoveries? Had these patients been left alone, what would have been their fate? Does the well-known sensitivity of this technology lead us to treat problems that are of no great import?

Would the Problems Have Been Recognizable by Other Means?

Routine dye curves, pressure measurements, and oxymetric data all provide different types of information but can be performed on a fairly routine basis. However this can be time consuming and the data lack the specificity and sensitivity of echo-DCFI. A complete epicardial echo-DCFI evaluation takes an average of 3.6 minutes and provides images of exceptional clarity.[7,9] Defects of questionable physiologic significance are often clearly discernible.[5,9,10] For example Figure 6 reproduces the dye curve obtained from the patient in Figure 4. Although the dye curve is consistent with "no shunt," this patient's residual VSD was classified as a "residual defect of concern." This was a fairly consistent finding—only extremely large defects produced abnormal dye curves. Further studies are in progress to quantitate these findings.

How Significant Are These Defects?

Table 3 demonstrates that patients who are allowed to leave the operating room with a residual defect of concern, as identified by echo-DCFI, have a disturbingly higher need for reoperation, or they die in the immediate postoperative period. Of particular interest are the data displayed in Table 4. Eighty-five per cent of patients with initially unacceptable results (by echo) who had immediate revision in the operating room had an acceptable outcome, whereas only 19% of a similar group of patients who did not receive immediate, successful revision had an acceptable outcome. The defects uncovered in these two groups were comparable. The clear implications of these findings are that echo-DCFI can disclose problems with a repair that may not be clinically apparent but which, if not fixed, can become important factors in the quality of survival for that patient. It can be predicted that the group of patients whose problems were recognized and repaired before they left the operating room would have had a similar, significant rate of reoperation had these anatomic imperfections (which were detectable only by echo-DCFI in the majority of cases) not been successfully corrected before they left the operating room. Furthermore the images produced by echo-DCFI can not only indicate a potential problem but they can also demonstrate the precise location and nature of the problem in relation to the reconstructed regions. This helps to guide the surgeon to perform efficient and accurate revision if necessary.

TABLE 4. *Intraoperative Echo-DCFI for Congenital Heart Repair: Impact of Residual Defect by Echo*

	N	Acceptable Outcome	Reop.	Surg. Death	Late Death
Repair before leaving OR	26	22	1	2	1
No repair before leaving OR	21	4*	10*	6	1

* $p < 0.0125$ by chi square (compared to repair before leaving OR). OR, operating room.

Epicardial echo-DCFI is an extremely sensitive method of examining ventricular function. Contractility and chamber dimension of each ventricle can be compared to preoperative status. Although it is the goal of an efficient procedure to produce an accurate reconstruction without damaging cardiac function, 25% of the patients in this series had some alteration of ventricular function (by echo) immediately after CPB. This was not always clinically significant and did not always require treatment. Furthermore the finding of decreased contractility was not necessarily an indication for inotropic therapy, but had to be considered within the context of the physiology of the cardiac lesion. For example decreased right ventricular contractility in an infant with pulmonary hypertension was sometimes best treated with hyperventilation. The usefulness of echo findings in directing intraoperative management has been previously described.[3-7,11-13] The data from this study imply that the presence of any change in ventricular function, for any reason, is associated with a higher incidence of early (but not late) postoperative death. This was especially true for patients with evidence of global (biventricular) dysfunction. Patients who toler-

TABLE 5. *Intraoperative Echo-DCFI for Congenital Heart Repair: Outcome Relating to Final Echo Results in 273 Patients*

Ventricular Function (Echo)	N	Acceptable Outcome	Reoperated	Surgical Death	Later Death
No RV or LV problem	205 (75%)*	180 (88%)	11 (5%)	8 (4%)	6 (3%)
Only RV problem	15 (5%)*	8 (54%)†	2 (13%)	5 (33%)†	0
Only LV problem	40 (15%)*	24 (60%)†	5 (13%)	10 (25%)†	1 (2%)
Both RV and LV problems	13 (5%)*	4 (31%)†	0	9 (69%)†	0

* Of entire series.

† $p < 0.004$ by chi square (compared to no RV or LV problems).

RV, right ventricle, LV, left ventricle.

ated their operative procedure without any change in cardiac function had an excellent (88%) chance of an acceptable long-term outcome.

If the operation is completed and post-CPB echo-DCFI fails to raise any concern about the result, the prognosis for a good outcome is greater than 90% (Table 6). However if there is any concern regarding the postrepair study, the likelihood of a good outcome is substantially decreased and may approach 50%. All data that led to the generation of these tables was provided prospectively, in the operating room at the time of surgery. This means that the surgeon who becomes familiar with the interpretation of echo-DCFI has the ability to quickly generate predictive information about the quality of the operative repair before the patient leaves the operating suite. Furthermore the nature of this information guides a direct and efficient modification of the procedure, where appropriate, to mend a residual defect or to revise a technical inaccuracy.

Because this method of evaluation provides qualitative rather than quantitative information, there is some subjectivity involved in interpreting the images. Other investigators who have used echo with or without DCFI to analyze results of congenital heart repairs in the operating room have found that small residual lesions frequently exist after surgical correction.[7,9-11,14] This is ascribed to the exquisite sensitivity of the technology and these findings have been generally believed to carry little significance.

Nevertheless, along this continuum, a defect can exist that may indicate a surgically unacceptable result. In most published series, post-CPB echo uncovers significant residual problems that are not otherwise apparent but require revision of the surgical procedure in 3% to 10% of patients. To date there have been no data to prospectively evaluate what might happen to those patients if the echo-identified problems were not revised. The question addressed by this study is: Can a surgical team learn to interpret their intraoperative echo-DCFI data in such a fashion that they can (1) predict the types of problems, disclosed by echo-DCFI, that might be associated with a higher incidence of postoperative complications or death, and (2) demonstrate this by comparing the outcomes for patients with residual problems of concern depending on whether these problems were adequately addressed in the operating room. The subjectivity of these methods is lessened by increased experience on the part of the team evaluating the data. As patients are followed and outcomes are compared to initial impressions of the intraoperative echo, what constitutes an "echo problem of concern" soon becomes apparent to all members of the team.

In this series only patients undergoing correction of congenital heart defects through a median sternotomy on CPB are reported. The study does not include patients undergoing other procedures, such as those performed through a thoracotomy (*e.g.*, PDA ligation, shunts, coarctation repairs, and so on). However the usefulness of echo-DCFI in this latter group of patients can also be explored. Although it is difficult to demonstrate in objective terms, it was strongly believed that the information provided by echo-DCFI shortened the learning curve by teaching the surgical team where problems occurred and gave immediate positive reinforcement of techniques that avoided these problems in subsequently treated patients.

There is no substitute for surgical skill, experience, and judgment in the repair of congenital heart defects. However the data from this investigation suggest that intra-

TABLE 6. *Intraoperative Echo-DCFI for Congenital Heart Repair: Outcome Relating to Final Echo Results in 273 Patients*

Any Residual Echo Concern	N	Acceptable Outcome	Reoperated	Surgical Death
No problems of concern	187 (68%)*	170 (91%)	6 (3%)	7 (4%)
Problems of concern	86 (32%)*	46 (54%)†	12 (14%)†	25 (29%)†

* Of entire series.

† $p < 0.0125$ by chi square (compared to no problems of concern).

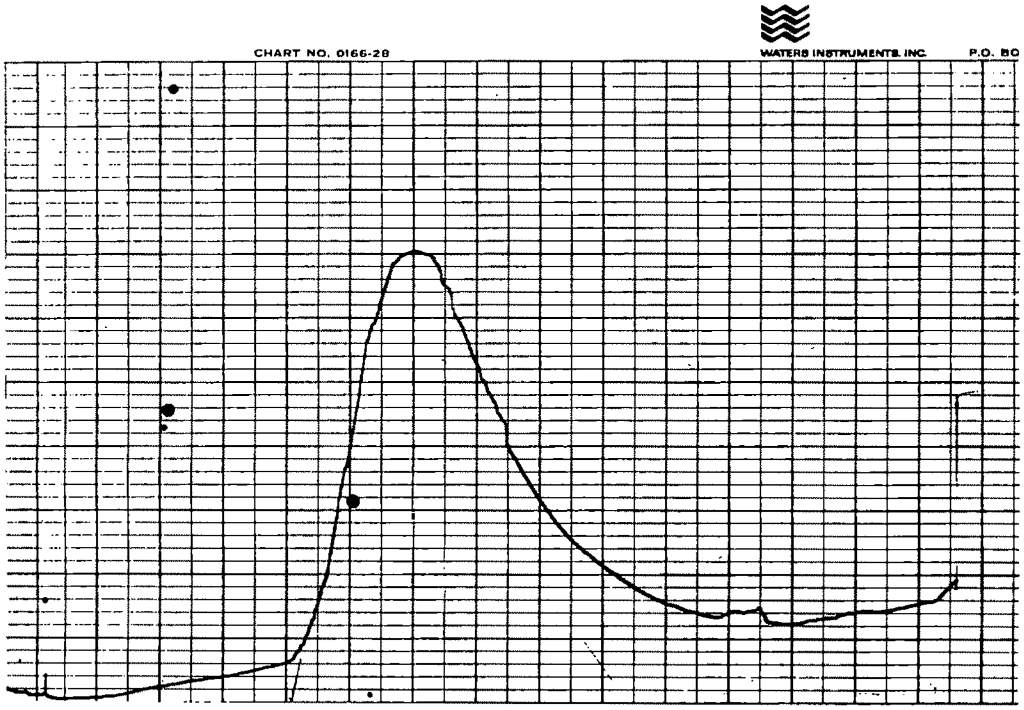

FIG. 6. Green dye curve obtained after CPB from the patient whose postrepair residual VSD is demonstrated in Figure 4. This dye curve was interpreted as demonstrating "no significant shunt."

operative echo-DCFI can be an invaluable tool for the refinement of these attributes by providing the surgeon with immediate information regarding the quality of the operative repair. Effective methods are reinforced and unsatisfactory results can be recognized in a timely fashion, enabling correction of problems before they affect the quality of patient survival.

Conclusions

Intraoperative epicardial echo with DCFI is a safe, quick, sensitive, and specific method to evaluate repair of congenital heart defects in infants and small children.

Echo with DCFI can provide information that can prevent patients from leaving the operating room with a suboptimal repair, especially if they have no clinical problems (7% of the patients in this series).

Patients who leave the operating room with echo defects of concern have a greater likelihood of requiring reoperation.

Patients with any change in ventricular function, by echo, after cardiopulmonary bypass have a higher incidence of early (but not late) postoperative death.

Patients who leave the operating room without any discernible problems on the postrepair echo have the best chance for an acceptable outcome (more than 90% in this series).

Acknowledgments

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DISCUSSION

DR. RONALD J. STONEY (San Francisco, California): As a noncardiac surgeon, I am interested in this paper that was beautifully presented because it really emphasizes what I think we are now able to apply certainly in the entire vascular tree to analyze technical results during operation.

We have not used the color flow system, but a duplex scan system in carotid and major aortic and aortic branch reconstructions for more than 5 years at our center.

I have just a few comments about this technology. It is extraordinarily sensitive and, using the technique of endarterectomy in the peripheral vasculature, for example, and I am sure this would apply to the intricate repair of the valves and also the outflow tracts of the heart, a number of defects appear on the postrepair that are discerning to the surgeon. He does not think that the imaging reflects the kind of an operation he did, and yet he looks at it and the data are undeniable.

We classify defects into minor and major. We repair major defects that were flow limiting to the kidney or viscera or brain, and did not repair minor defects that had flaps that were proximally based or were minor disturbances of the intimal surface. I wonder if we could learn from Dr. Ungerleider and his experience what types of defects he chose not to repair because, from his presentation, 27 of the more than 40 defects he detected were, in fact, repaired during operation with very good outcome, and a number of the patients who left the operating room unrepaired with detected defects did not do as well.

What are his criteria for looking at a defect and choosing to go back and reopen the heart, or in our case the vessel, and attending to the technical chores that are necessary?

DR. ALDEN HOOD HARKEN (Denver, Colorado): It is a delight to see Dr. Ungerleider and the group from Duke assimilating new technologies to help us address major problems in the operating room. We have learned throughout this meeting that as surgeons we need to do this, everything from lithotripsy devices to staplers, which can help us ask these kinds of important questions.

Ross I would like to ask you a couple of questions. First a purely practical one of looking at very small hearts. Is this a major problem in the operating room? Have you been able to convince your cardiology colleagues to use this in the catheterization laboratory after a balloon valvotomy? Following up on some of the pioneering work that has come out of the Duke cardiac surgical laboratories on differences between myocardial metabolism in neonates *versus* adults, have you been able to use this as a functional measure early or late after operation to assess some of the observations that you and your colleagues have developed trying to discriminate methods of myocardial preservation or protection?

You and Dr. Wechsler called our attention to the fact that with myocardial maturation there are increasing concentrations of 5′ nucleotidase in myocardium and that has piqued many of us into thinking of ways of tailoring a substrate preservation intracellularly.

One of our problems, however, has been a difficulty in quantitating or objectively assessing myocardial function in the early postischemic, postperfusion period. Have you been able to use this new technique to help us ask some of those critically important questions?

DR. HILLEL LAKS (Los Angeles, California): Dr. Ungerleider and his colleagues from Duke are to be commended for an excellent prospective study that evaluates the routine use of intraoperative echocardiography in congenital cardiac surgery, and they have found that the finding of a residual defect was associated with increased rates of early and late mortality.

We also, with the collaboration of our pediatric cardiologists, Dr. Roberta Williams and Dr. Tom Santuti, have used intraoperative echocardiography as part of our assessment of the postoperative repairs. We have found, as others have, that small residual ventricular septal defects are not uncommon. However within a period of several days, these defects are closed.

The differentiation, however, between moderate and large defects is much more difficult, and I would wonder if Dr. Ungerleider could comment on the use of more traditional methods of assessing these residual defects, such as left and right ventricular pressure ratios and oximetry. Have these indices correlated with the findings of intraoperative echocardiography?

The color flow doppler has perhaps been most useful in assessment of valve repairs, and we have found this extremely useful both for aortic and mitral valve repairs.

Zair and the group from Cedars Sinai have found that although there was excellent correlation between angiographic assessment of mitral regurgitation, there was little correlation between the surgical assessment by means of saline distention of the ventricle and the intraoperative echo. Could Dr. Ungerleider comment on their findings of the surgical assessment and the intraoperative echo after coming off bypass?

The costs of intraoperative echo are not negligible. The machine costs about $200,000. There is about a $460 charge for the study and an experienced technician may be occupied for as long as one hour. Should these studies, therefore, be done in a more selective manner when problems in the intraoperative repair have been identified by more conventional methods such as pressure measurement and oximetry? On the basis of your experience, do you still recommend that this be done on a routine basis or could it be used on a more selective basis for specific repairs?

I would like to ask whether the transesophageal echocardiogram, which the Duke Group has used extensively in adults, has advantages over the epicardial echocardiogram.

The group from Cincinnati has used a transesophageal probe for children from the age of 7 years, but in smaller children it would be even more valuable. A smaller probe so far has not been available.

DR. ROSS UNGERLEIDER (Closing discussion): I think the discussants have picked up on the main issues that revolve around the use of this technology in the operating room.

Dr. Stoney mentioned that the sensitivity of this instrument has been well recognized even when it has been used in other areas of surgical therapy. It is a remarkably sensitive instrument, and the reason that we embarked on this study was to find out if the instrument is too sensitive to be useful in this manner. That is why the defects were coded as best as they could be into areas of acceptability or unacceptability. Certainly that is a subjective categorization. The technology is exquisitely sensitive, and it is remarkable how many good repairs are not "echo-perfect." Nevertheless the results of this study suggest that it is possible to predict which residual lesions tend to correlate with a poorer long-term outcome. This is perhaps particularly relevant when we look at the second part of his question. That is, which defects do we choose not to repair.

In this series we tried to obtain the best echo results that we could within reason. Because we did not initially know what would be the outcome for various residual echo defects, we chose not to revise defects that would require taking down part of the repair to get to (*i.e.*, removing a conduit to get to a residual VSD) as well as defects in patients whose length of operation or general condition suggested that they might not tolerate prolongation of the procedure or an additional period of cardiopulmonary bypass. We also were lenient with respect to residual mitral regurgitation after AV canal repair because we know that it is usually well tolerated and to repair it would require taking down a portion of the repair. We have followed the fate of patients with these unrepaired defects to see if it differed from patients whose similar residual problems were repaired before leaving the operating room. This was the closest we could come to a "control" and the results from this study suggest that once surgeons learn to recognize the degree of residual echo defect that correlates with reduced quality of survival, a more aggressive attempt at correction before leaving the operating room may be warranted.

Dr. Harken asked the question about the usefulness of this technology in looking at ventricular function. It is very useful in looking at ventricular function, but it does not quantitate ventricular function as well as sonor micrometric methods, so for now the best way to assess ventricular performance, especially experimentally in neonates with respect to myocardial preservation techniques, is probably using sonomicrometry or high-energy phosphate metabolism.

Dr. Laks' questions regard subjectivity of this method and whether we correlated any of our data with other more common methods. If I could for just a moment show slide 44, I think in answer to Dr. Laks' question we can show that there were residual defects such as this particular one (same as Fig. 4). This was a moderate residual ventricular septal defect by echo standards, and was considered to be unacceptable.

The next slide shows the dye curve that was obtained from that patient (same as Fig. 6), and this is read as a normal dye curve, so that there was no significant left-to-right shunt from that lesion. This again attests to the sensitivity of this technology.

We are accumulating further data like this and we hope that we will be able to provide it in a subsequent report.

Echo is very sensitive for assessing mitral regurgitation, more sensitive than any other method we know of, and so we used that information very carefully when determining whether to do anything about mitral valves.

The transesophageal approach is certainly very valuable. It allows online information to be obtained while the surgeon is working, but the transesophageal approach is not applicable at this time with current technology to the small babies and children, the majority of patients operated on in this series. We have recently been asked to evaluate a smaller esophageal probe, marketed by Corometrics (Wallingford, CT), and have used it for babies as small as 8 kg. The technology in this area should continue to improve. In addition the various view orientations that can be obtained by the surgeon, using the epicardial approach, are very valuable for the complexity of lesions that are found in congenital heart defects.

Finally, with respect to the cost of this technique, we have found ways to reduce the cost and make it more cost-effective by leaving the transducer over the screen while the machine can be removed from the operating room and brought to other areas in the operating suites or in the hospital as it is needed during the time the operation is taking place. The machine is then returned to the operating room at the conclusion of the procedure so that it is available for the postrepair exam.

It does take a tremendous amount of commitment on the part of the personnel who can train surgeons to use this technique, but once a surgeon learns how to do an epicardial echo, the cost-effectiveness is great because it requires very little time. Furthermore the specificity and sensitivity make it far more valuable than other methods of evaluating repair, so we believe that once learned, surgeons will prefer to use the technology routinely in lieu of the other less helpful alternatives.

The Results of Esophagogastrectomy Without Thoracotomy for Adenocarcinoma of the Esophagogastric Junction

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Between 1980 and 1988, 98 patients with adenocarcinoma of the esophagogastric junction were seen at the University of Western Ontario. Eighty-two patients underwent resection of the celiac lymph nodes, lesser curve and cardia of the stomach, and thoracic esophagus through abdominal and neck incisions avoiding thoracotomy. The esophagus was replaced by a stomach tube in 80 patients or by a colon tube in two patients. Two of 82 patients died while hospitalized. Early postoperative morbidity included anastomotic leaks that closed spontaneously (13), transient hoarseness (10), myocardial infarction (2), pulmonary embolus (6), and atelectasis or pneumonia (13). Late postoperative complications included delayed gastric emptying (4), symptomatic reflux (4), diarrhea (10), and anastomotic strictures (17). The 2-year survival of 30% was significantly affected by the stage of disease (p = 0.003), depth of tumor penetration (p = 0.02), lymph node metastasis (p = 0.001), tumor differentiation (p = 0.008), and tumor DNA ploidy (p = 0.02). Local recurrences appeared initially in 20 patients: anastomotic (3), peritoneal (14), mediastinal (3); distant metastasis occurred in 27 patients: bone (15), liver (5), brain (2), and multiple organs (5). Swallowing was restored and maintained in 75 patients. Esophagogastrectomy without thoracotomy provides a safe, effective method of restoring swallowing in patients with adenocarcinoma of the esophagogastric junction. This technique provides acceptable survival and local recurrence rates.

ADENOCARCINOMA OF THE esophagogastric junction is one of the most difficult malignancies to cure. The patients usually present with dysphagia late in the course of the disease. At the time of diagnosis, there is often spread of the tumor to adjacent structures and regional lymph nodes.[1-3] If the disease is localized, surgical resection is considered the optimal treatment because resection provides a chance to remove all local disease for cure. If the disease is advanced at the time of diagnosis, effective palliation is the primary goal of treatment. Although there have been recent reports of promising regimens offering palliation and some chance for cure with radiation and/or chemotherapy,[4,5] the primary treatment modality for adenocarcinoma of the esophagogastric junction has been surgery.

Controversies connected with operations for adenocarcinoma of the esophagogastic junction relate to the type and extent of resection to be performed. The classical operations carried out for this tumor include total gastrectomy,[2] or partial esophagogastrectomy done through either a thoracoabdominal incision on the left side,[6] a left thoracotomy with incision of the diaphragm,[3] or a laparotomy and right thoracotomy.[7] Death associated with these operative techniques is usually due to anastomotic leaks into the pleural cavity or mediastinum or respiratory complications.[8,9] Because these cancers often spread submucosally up the esophagus, there is a high incidence of residual tumor at the proximal resection line, with associated gross tumor recurrence.[7] Furthermore when the esophagogastric anastomosis is carried out within the thoracic cavity, regurgitation and reflux esophagitis are common.[7]

With the aim of minimizing these complications, and reducing operative mortality for the past 8 years, we have treated adenocarcinoma of the esophagogastric junction with *en bloc* resection of the lesser curvature and cardia of the stomach, celiac lymph nodes, diaphragmatic crura, and the thoracic esophagus. The esophagus is replaced by a tube made from the greater curve of the stomach or colon, which is brought through the posterior mediastinum and anastomosed to the cervical esophagus. The procedure is done through an incision in the upper part of the abdomen and left neck, thus avoiding thoracotomy and intrathoracic anastomosis. The purpose of this report

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TABLE 1. *Gastric Staging*

TNM Clinical Classification

T—Primary tumor

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ:* intraepithelial tumor without invasion of the lamina propria
T1	Tumor invades lamina propria or submucosa
T2	Tumor invades muscularis propria or subserosa
T3	Tumor penetrates the serosa (visceral peritoneum) without invasion of adjacent structures
T4	Tumor invades adjacent structures

N—Regional Lymph Nodes

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in perigastric lymph node(s) within 3 cm of the edge of the primary tumor
N2	Metastasis in perigastric lymph node(s) more than 3 cm from the edge of the primary tumor or in lymph nodes along the left gastric common hepatic, splenic, or coeliac arteries

M—Distant Metastasis

Stage Grouping

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T1	N1	M0
	T2	N0	M0
Stage II	T1	N2	M0
	T2	N0	M0
	T3	N0	M0
Stage IIIA	T2	N2	M0
	T3	N1	M0
	T4	N0	M0
Stage IIIB	T3	N2	M0
	T4	N1	M0
Stage IV	T4	N2	M0
	Any T	Any N	M1

is to document the risks and effectiveness of the operation and to evaluate factors responsible for tumor recurrence and death.

Materials and Methods

Adenocarcinoma of the esophagogastric junction is defined as an adenocarcinoma arising in the upper one third of the stomach and involving the esophagogastric junction or an adenocarcinoma in a columnar-lined esophagus involving the esophagogastric junction. Adenocarcinomas arising in the fundus, diffuse cancers of the linitis plastica type, and squamous cell carcinomas of the esophagus were excluded from the study.

Between 1980 and 1988, 98 patients with adenocarcinoma of the esophagogastric junction were seen at the University of Western Ontario. Seven patients had conservative management because of advanced distant metastases or medical contraindication to operation. Ninety-one patients had laparotomies as the first step of a planned resection. In nine of these patients the tumor was nonresectable because of invasion of the aorta by the tumor,[3] peritoneal metastasis,[4] and multiple liver metastasis.[2] The remaining 82 patients underwent resection of the celiac lymph nodes, lesser curve and cardia of the stomach, and thoracic esophagus through abdominal and neck incisions, thus avoiding thoracotomy. The esophagus was replaced by a tube fashioned from the greater curvature of the stomach in 80 patients and left colon in two patients. No patients received postoperative chemotherapy and four patients received postoperative radiotherapy for residual disease.

After surgery the patients were evaluated at 3-month intervals until the time of this writing or death. The site and the time of the first recurrence of cancer and the long-term complications were carefully documented during the evaluation visits. No patients were lost to follow-up.

Statistics

Actual survival analysis was performed using the Kaplan-Meier product limit estimates and comparison of survival curves were evaluated using the Mantle-Cox test. Multivariate analysis was performed using Cox regression analysis. Statistical significance was defined as $p < 0.05$ for Mantle-Cox and $p < 0.15$ for Cox regression analysis.

Pathology

Tumors were evaluated for differentiation, depth of invasion, size, vascular invasion, lymph node involvement, flow cytometric DNA analysis, and the presence of a columnar-lined esophagus. Pathologic staging was performed according to the U.I.C.C. staging system for gastric carcinoma (Table 1).

Local recurrence was considered to occur if there was convincing evidence of recurrence of cancer at the site of the anastomosis, in the posterior mediastinum, or in the peritoneal cavity.

Systemic recurrence occurred when there was evidence or recurrence of cancers in the cervical lymph nodes, liver, lung, bone, or brain.

Preoperative Staging and Care

After the clinical examination, histologic diagnosis of the tumor was made by endoscopic biopsy. Distant metastasis were ruled out. Since 1983 all patients have had a CT scan of the chest and upper abdomen to determine the size and extension of the tumor.

Nutritional status was assessed in all patients. Those patients who lost more than 10 pounds or demonstrated hypoalbuminemia were given enteral or parenteral alimentation at least 1 week before the operation. Clinical contraindications to operation included diminished pulmonary function with a forced expiratory volume at 1 second of less than 1 L or evidence of uncontrolled congestive heart failure.

Operative Technique

The goals of this operation are to remove completely the celiac lymph nodes, the lesser curvature of the stomach around the tumor, the cardia, the tumor, the intrathoracic esophagus, as well as any adherent local structures such as the diaphragmatic crura. Extrathoracic anastomosis minimizes the harmful effects of an anastomotic leak by permitting drainage of gastrointestinal contents out of the neck drain. A further aim is to decrease the incidence of tumor recurrence at the site of anastomosis by removing the intrathoracic esophagus. Finally by avoiding a thoracotomy we anticipated a decreased incidence of respiratory complications.

Under general anesthesia, a double lumen tube is placed in the tracheobronchial tree so that, if the chest had to be entered, one of the lungs can be collapsed. The abdomen, right chest, and left side of the neck are then prepared and draped. The abdomen is entered through an upper midline incision and the resectability of the tumor is determined. If the tumor is resectable, the stomach is completely mobilized by dividing the gastrocolic omentum while preserving the right gastroepiploic vessels. The gastrohepatic omentum is then divided close to the liver. The left gastric artery and vein are identified, ligated, and divided. Celiac and left gastric lymph nodes are removed and the diaphragmatic crura of the hiatus are resected in continuity with the esophagogastric junction. With the retraction of the enlarged hiatus, the lower part of the esophagus and surrounding pleura are dissected under direct vision up to the carina, and all vessels to the esophagus are clipped and divided. The vagus nerves are divided just below the carina. During this intrathoracic dissection, care is taken not to compress the heart and decrease the venous return.

Attention is then turned to the neck where an incision is made along the left sternocleidomastoid muscle down to the suprasternal notch. The middle thyroid vein is ligated and divided and the cervical esophagus is exposed and isolated, taking care not to injure the recurrent laryngeal nerves. The thoracic esophagus is carefully dissected from the back of the trachea, clipping all arterial branches going into the esophagus. The cervical esophagus is then divided and the proximal end of the distal portion of the esophagus is delivered into the abdomen. Any vessels that are left going into the esophagus can be exposed, clipped, and divided through the hiatus. The duodenum is then well mobilized and a pyloromyotomy is carried out. A tube, approximately 3 cm to 4 cm in diameter, is then made from the greater curve of the stomach using a stapling device. Care is taken to excise the lesser curve of the stomach as well as at least 4 cm of normal stomach around the tumor. The staple line of the gastric tube is inverted with nonabsorbable sutures.

The stomach tube is brought up through the posterior mediastinal esophageal bed to the neck and sewn to the prevertebral fascia and an end-to-end or end-to-side anastomosis is then carried out between the cervical esophagus and stomach using a two-layered anastomosis. The gastric tube is brought up in the retrosternal position if gross tumor is left behind to avoid local recurrence into the gastric tube.

A nasogastric tube is then placed across the anastomosis into the stomach for decompression. A chest tube is placed in the pleural cavity if the pleural space is violated. A small drain is placed close to the cervical anastomosis and brought out through the skin. A feeding jejunostomy is usually carried out for early postoperative nutrition.

Postoperative Care

Most patients are extubated after the operation. Prophylactic antibiotics are given before operation and for 48 hours after the operation. Jejunostomy tube feedings are started three days after the operation. A gastrograffin swallow is carried out seven days after operation. If there is no anastomotic leak, the nasogastric and chest tubes are removed. If a leak is shown, the patient is given nothing by mouth for another five days and then begun on an oral diet. All fistulas closed spontaneously with no operative intervention. This operative technique has been described in detail by our group in a previous paper.[10]

Results

There were 72 men and 10 women, with a median age of 62 years (range, 37 to 81 years). Presenting symptoms in the 82 patients included dysphagia (69), weight loss greater than 10 pounds (56), heartburn (31), regurgitation (27), odynophagia (18), and bleeding (4). Significant preoperative risk factors included previous myocardial infarction (8), ventricular arrhythmia (5), smoking (68), chronic obstructive pulmonary disease (11), diabetes (8), thromboembolic disease (3), and heart failure (2).

Mortality and Morbidity (Table 2)

There were two hospital deaths, both from pulmonary emboli, 14 and 15 days after operation. The patients took a median time of 11 days before they began eating a solid diet and the median time to discharge was 15 days.

Twenty-three patients had one or more complications in the postoperative period. Eleven patients developed a new arrhythmia and two of these patients had an associated myocardial infarction. Six patients had a documented pulmonary embolus after the operation. Seven patients required more than 24 hours of mechanical ventilation after the operation. Thirteen patients had atelectasis and/or pneumonitis in the postoperative period.

TABLE 2. *Early Complications of the Resection*

Complication	Number	Per Cent of Resected Patients
Azygos vein tear	1	1
Cardiac arrhythmia	11	13
Pulmonary embolus	6	7
Myocardial infarction	2	2
Atelectasis or pneumonitis	13	16
Respiratory failure	7	9
Anastomotic leak		
Radiographic diagnosis only	8	10
External fistula	5	6
Transient hoarseness	10	12
Delayed gastric emptying	4	5
Dysphagia	17	20

Ten patients developed transient hoarseness. One of these patients had a permanent left vocal cord paralysis. One patient had an intraoperative hemorrhage from a tear in a branch of the azygos vein requiring a right thoracotomy to stop the bleeding. Eight patients had an anastomotic leak documented by gastrograffin swallow that did not drain externally. Five patients developed an early fistula from an anastomatic leak. All of the anastomotic leaks closed spontaneously with conservative management. Four patients had temporary delayed gastric emptying but no patients required a pyloroplasty to supplement the pyloromyotomy. No patients developed chylothorax, subphrenic abscess, empyema, or required an incidental splenectomy at the time of operation.

Seventeen of the surviving patients needed an esophageal dilatation in the postoperative period. Five patients required more than three esophageal dilatations to maintain swallowing. Three months after the operation, 94% of the patients were swallowing at least a soft diet (Table 3). Four patients complained of symptomatic reflux in the supine position. Postprandial diarrhea was controlled by a postgastrectomy diet in ten patients.

Pathology (Table 4)

Adenocarcinoma was found in association with a columnar-lined esophagus in 28 of the 82 patients. Tumor differentiation was accurately examined in 76 patients. Twenty-one patients had a well- differentiated tumor, 21 patients had a moderately differentiated tumor, and 34 patients had a poorly differentiated tumor. Of the 75 tumors that underwent flow cytometric DNA analysis, 61 tumors were aneuploid and 14 tumors were diploid. Vascular invasion was seen in 37 of 73 tumors. Lymph node metastases were found in N1 nodes in 35 patients and in N2 nodes in 26 patients. Twenty-one patients had no lymph node metastases. There was partial esophageal wall invasion in 28 patients (T1 or T2) and 64 patients had full-thickness involvement. Using the UICC gastric staging technique, 12 patients were stage I, 18 patients were stage II, 47 patients were stage III, and 5 patients were stage IV.

Survival

The overall survival rate for the resected group was 55% at 1 year and 31% at 2 years (Fig. 1). The median survival time was 16 ± 1 month. The disease-free survival rate was 46% at 1 year and 23% at 2 years.

The 2-year survival for patients with stage I and II disease was 50% and that of patients with stage III and IV disease was 21% ($p = 0.003$). The 2-year survival rates for each stage were stage I, 73%; stage II, 37%; stage III, 21%; there were no 2-year survivals in stage IV ($p = 0.001$; Fig. 2).

Patients with a columnar lined esophagus had a slightly better 2-year survival rate of 45% compared to patients with no associated columnar-lined esophagus whose survival rate was 25% at 2 years ($p = 0.1$).

The 73% 2-year survival rate for patients with well-differentiated tumors was significantly different than those with moderate (23%) and poorly differentiated tumors (15%) ($p = 0.008$).

The 2-year survival rate for patients with partial esophageal wall invasion (46%) was significantly different than those with full- thickness invasion (23%; $p = 0.02$). Two-year survival rate for the 21 patients with no metastasis (53%) was significantly better than the survival rate for patients with positive lymph node metastasis (21%) ($p = 0.001$). Two-year overall survival of patients with diploid tumor was 66% compared to 9% for aneuploid tumors ($p = 0.02$).

Using Cox regression analysis, the significant prognostic independent variables for predicting overall 2-year survival from adenocarcinoma of the esophagogastric junction were tumor differentiation ($p = 0.08$), depth of wall invasion ($p = 0.03$), and lymph node metastasis ($p = 0.001$).

Tumor Recurrence

Forty-seven patients have developed a recurrence of their cancer (Table 5). The median time from the operation to the recurrence of the tumor was 11 months. Twenty patients recurred locally either at the anastomosis (3) or in the esophagogastric bed (17). All of these patients

TABLE 3. *Late Complications of the Resection*

Complication	Number	Per Cent of Surviving Patients
Dysphagia	5	6
Gastroesophageal reflux	4	5
Postprandial diarrhea	10	13
Recurrent nerve paralysis	1	1

TABLE 4. *Pathologic Features*

	Number of Resected Patients	Median Survival Time (Months)	Per Cent of Patients Who Survived 2 Years	p Value
Overall		13	31	
Stage				
I	12	24	73	0.001
II	18	18	37	
III	47	11	21	
IV	5	6	0	
Lymph node metastasis				
Yes	61	12	21	0.001
No	21	39	53	
Depth of penetration				
Partial thickness	28	22	46	0.02
Full-thickness	64	11	23	
Tumor differentiation				
Well	21/76	24	73	0.008
Moderate	21/76	14	23	
Poor	34/76	9	15	
DNA ploidy				
Diploid	14/75	22	66	0.02
Aneuploid	61/75		9	
Columnar-lined esophagus				
Yes	28	16	45	0.1
No	54	11	25	

either had lymph node metastasis or transmural spread of their tumor at the time of resection. Two of the three patients with anastomotic recurrences had microscopic evidence of tumor in their gastric resection margins. Twenty-seven patients had tumor recurrence in the bone, liver, or brain.

Palliation

Before operation 69 of the 82 patients could not eat solids and of these, 27 also had difficulty swallowing liquids. Fifty-six patients had lost more than 10 pounds in weight. Of the 80 patients who survived the resection, 17

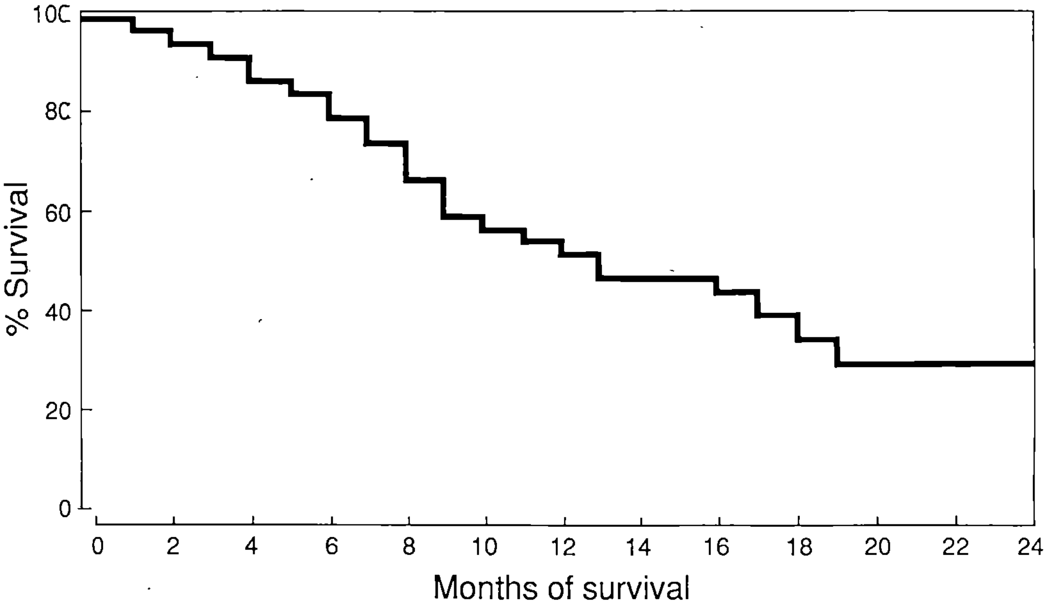

FIG. 1. Overall survival rates of 82 patients with resected adenocarcinoma of the esophagogastric junction. Operative deaths are included.

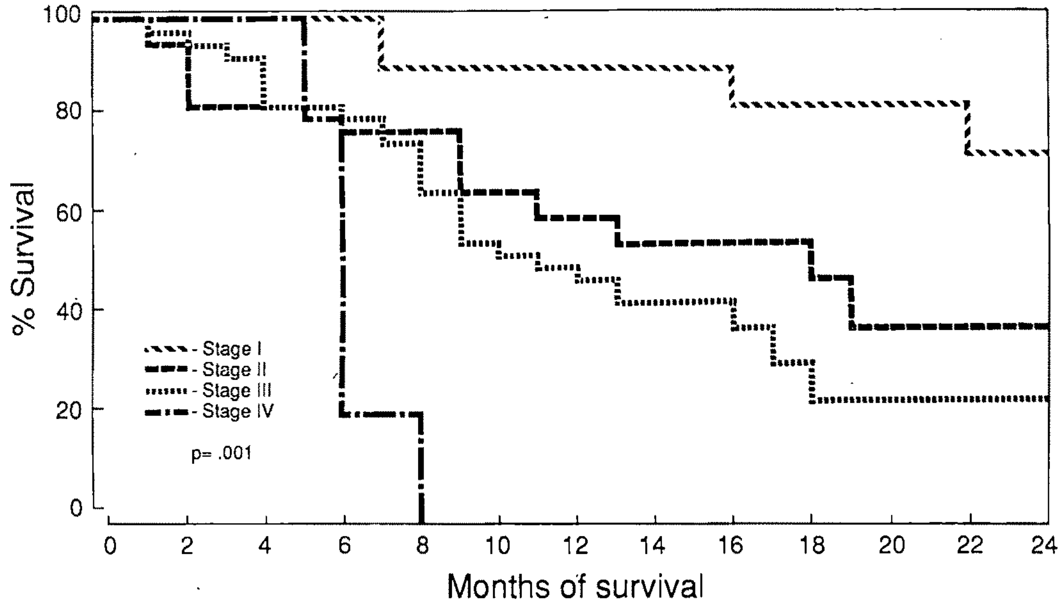

FIG. 2. Overall survival showing a significant difference in survival rates between the stages.

patients required esophageal bouginage to swallow a soft diet. Five of these patients required more than three bouginages, two on a chronic basis secondary to reflux esophagitis. Three patients developed dysphagia for solids at 10, 11, and 14 months after the operation because of recurrent tumor at the anastomosis. Swallowing was maintained until the present time or death in 75 patients. Six patients could not gain weight in the early postoperative period because of anastomotic structures[4] and delayed gastric emptying.[2]

Discussion

The ideal operation for adenocarcinoma of the esophagogastric junction should relieve dysphagia, bleeding, and pain with minimal morbidity and mortality. Furthermore there should be complete resection of the tumor and surrounding tissues to avoid local recurrence and improve long-term survival. Transhiatal esophagogastrectomy without thoracotomy, popularized by Orringer in North America,[11] has been criticized as a dangerous operation that contravenes the basic surgical principles of adequate exposure and *en bloc* resection of cancer.[12] The hospital operative mortality rate of 2.4% in this series equals the best operative mortality rates for partial esophagogastrectomy[3,13] and is better than operative mortality rates for total gastrectomy,[2,14] and *en bloc* resection.[15] Most of the deaths in these other series have been due to leaking of the anastomosis into the mediastinum and respiratory complications.[8,9] Although 13 patients have evidence of anastomotic leaks on x-ray examination in this study, only five developed fistulas. The harmful effects of the anastomotic leak were minimized by drainage of gastrointestinal contents out of the neck drain. All the anastomotic leaks closed spontaneously. The incidence of pulmonary complications was no different than that reported for partial esophagogastrectomy and total gastrectomy.[8,9] However, unlike Postlethwait's report,[9] there were no deaths from pneumonia in this study. The two deaths in this series resulted from pulmonary emboli occurring 14 and 15 days after the operation. Four more patients had nonfatal pulmonary emboli. The high incidence of pulmonary emboli in this series suggests that the use of prophylaxis against venous thrombosis is indicated during the hospital stay. Cardiac dysrhythmias were common after this operation. Thirty-two patients developed supraventricular tachycardias. Eleven of these patients had evidence of atrial fibrillation and two had an associated myocardial infarction. This high incidence of cardiac dysrhythmias could be secondary

TABLE 5. *Site of First Cancer Recurrence*

	Number	Per Cent of Recurrences
Local recurrence	20	43
Anastomosis	3	
Peritoneal	14	
Mediastinal	3	
Distant recurrence	22	47
Bone	15	
Liver	5	
Brain	2	
Synchronous local and distant recurrence	5	10

to retraction of the pericardium at the time of surgery, intravascular volume changes, or pericarditis.

Although there is complete resection of the intrathoracic esophagus, lesser curve of the stomach, and the celiac, left gastric, pericardiac, and lower mediastinal lymph nodes with this procedure, a potential disadvantage of this operation is the failure to clear completely the subcarinal lymph nodes.[10] However, Castrini's study[1] has shown that only 1% of adenocarcinomas of the esophagogastric junction have spread to the subcarinal lymph nodes at the time of resection. If resection of metastatic subcarinal lymph nodes is critical for long-term survival, then the frequency of incompletely removing these nodes with this operation is low and probably does not affect long-term survival. In this study 84% of the patients seen with adenocarcinoma of the esophagogastric junction underwent resection. This resectability rate was equal to that of Ellis'[3] and greater than that of all other reports.[2,6,13-15] The number of patients with either transmural spread of tumor or metastasis to the regional lymph nodes in this study was equivalent or greater than other reports.[2,3,13,15] Despite the frequency of advanced disease, 55% were alive 1 year and 31% were alive 2 years after the resection. Patients with early stage disease also had survival rates equivalent to those of Ellis[3] and Paolini[2] and better than the results of Skinner.[15] This survival rate suggests that resection of these early cancers was not compromised by the esophagogastrectomy without thoracotomy. In fact if the resectability rate, operative mortality rate, and survival statistics are taken into account, more patients in this study were alive at 2 years than in those studies where patients underwent total gastrectomy[2] or *en bloc* esophagogastrectomy.[15]

Adenocarcinomas at the esophagogastric junction often spread submucosally up the esophagus, leading to a high incidence of residual tumor at the resection margin. The resection of the total intrathoracic esophagus and lesser curve of the stomach in this series resulted in three local recurrences at the esophagogastric anastomosis. Unlike local recurrence occurring after total gastrectomy[2,14] or transthoracic esophagogastrectomy,[3,7] the site of recurrence appeared to be from the stomach in this study. The low incidence of recurrent tumor at the esophagogastric anastomosis is similar to that observed by Skinner[15] but lower than that observed with limited esophagogastrectomy[3] or total gastrectomy.[2,14] The anastomotic recurrences observed in this study could be avoided by more radical resection of the stomach as proposed by De Meester.[16] Besides the three patients who developed local anastomotic recurrences, 17 patients recurred locally in the esophagogastric bed or peritoneal cavity. This local recurrence rate is similar to that observed by Barber[17] after transhiatal esophagectomy for esophageal cancer and Gunderson[18] after radical gastrectomy for adenocarcinoma of the stomach. The latter reoperation series following curative resection suggested that the extent of the initial operative procedure had little effect on either the incidence or type of subsequent tumor recurrence. Lymph node failures were found in a high percentage of patients who supposedly had radical lymph node dissections. Thus all these data suggest that although systemic therapy is clearly important,[19] the development of an effective local therapy,[20,21] which is an adjuvant to surgery, could potentially benefit some patients with adenocarcinoma of the esophagogastric junction.

Analysis of treatments for adenocarcinoma of the esophagogastric junction suggests that outcome generally reflects the biologic behavior of the cancer rather than the extent of the operation. In this study, 2-year survival was significantly affected by the stage of disease, depth of tumor penetration, lymph node metastasis, tumor differentiation, and the nuclear DNA content of the tumor. Similar to observations by Ellis[3] and Skinner,[15] cancer arising in a columnar- lined esophagus had survival rates equal to adenocarcinoma of the cardia. Tumors with abnormal nuclear DNA content were associated with increased incidence of lymph node metastasis, advanced stage disease, and poorer survival. However using Cox regression analysis tumor ploidy was not an independent prognostic variable in predicting death from adenocarcinoma of the esophagogastric junction. This finding could be explained by the advanced stage of cancers observed in this report.

Before the esophagogastrectomy only 16% of the patients could swallow a solid meal. The 20% incidence of early postoperative dysphagia could be explained by scarring secondary to anastomostic leaks, ischemia, or gastroesophageal reflux. However 3 months after the operation 94% of the patients had normal swallowing restored and 90% maintained this diet until the time of this writing or death. Palliation provided by this operation was better than all other reported techniques for management of adenocarcinoma of the esophagogastric junction.[2,3,4,5,15]

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DISCUSSION

DR. F. G. PEARSON (Toronto, Canada): In a very short period of time a great deal has been presented in this 10-minute paper, and I can assure you that the information has been very thoroughly documented and evaluated. The results obtained in an impressively large series of well-staged consecutive patients are, in fact, as good or better than any other reported data on operative mortality, morbidity, and survival by stage in patients managed by resection with adenocarcinoma of the EG junction.

Importantly the survival data in these 82 patients managed by total thoracic esophagectomy without thoracotomy (or transhiatal esophagectomy) are as good or better than the best results using more extensive exposures and operative procedures that describe a more radical mediastinal dissection.

In Toronto we have had a fairly extensive experience with this technique of transhiatal esophagectomy beginning in 1960 with patients managed by gastric substitution after pharyngolaryngectomy, and for some years now we have used this approach in selected patients with adenocarcinoma at the esophagastric junction. I can confirm that with experience it is absolutely clear that adequate exposure of the distal esophagus from the hiatus to the carina can be achieved using appropriate techniques of retraction through the dilated hiatus. I would emphasize, as the diagram did, that the esophageal relationships are visualized, and vessels are ligated and divided under direct vision.

What are the advantages of this approach? The functional results obtained by using gastric substitution and a high esophagogastric anastomosis are very good. Indeed I don't think any other substitute provides such predictably good functional results. Reflux is a minimal problem. Should a leak occur, the cervical anastomosis is less morbid and potentially lethal than a leak from an intrathoracic anastomosis.

The potential for local recurrence is minimized, and with experience there is no simpler alternative operation. Indeed, if two surgical teams are used, this operation can regularly be done in less than 3 hours.

What are its disadvantages? There is a learning curve for the technicalities of the operation, but I am not certain that this is significantly more than for any other operation to remove the thoracic esophagus. There may be a bias to the limit of the extent of proximal gastric resection, and all three of Dr. Finley's local recurrences occured on the gastric side of the anastomosis. I would ask Dr. Finley to comment on your management of the level of proximal resection to minimize this problem of local recurrence.

I would also ask for comment on the complication of recurrent nerve palsy. Although transient, you report a high incidence. Do you have technical suggestions as to how this can be reduced? Finally how do you manage anticoagulation to try to reduce the incidence of pulmonary embolism that was also a rather frequent complication in this series?

I think this is a very important contribution and documents the effectiveness of this approach better than any other previous report.

DR. ROBERT E. CONDON (Milwaukee, Wisconsin): Our series is not as extensive, but in many ways is comparable, and I rise primarily to emphasize a couple of points. One is the relative safety of the cervical esophagogastric anastomosis. It really makes a remarkable difference, as compared with an intrathoracic anastomosis, in terms of both the morbidity and mortality risk of a leak. Second the cervical esophagogastric anastomosis avoids the very real problem in patients who survive more than 6 months of reflux esophagitis in the residual esophagus.

A patient with an intrathoracic esophagogastric anastomosis after a more classic left thoracotomy resective procedure, if that patient survives 6 months, is often very significantly disabled by reflux esophagitis; some patients cannot eat and their inability to maintain oral nutrition recurs, but on a different basis than before operation.

I would like to raise with Dr. Finley perhaps a minor point of disagreement. In patients who are not obviously so preterminal that we refuse operation, that is, in all patients whom we explore, we resect tumor regardless of the presence of peritoneal or liver metastases because our primary objective of the operation is palliation and restoration of ability to swallow food by the oral route. I wonder if Dr. Finley could discuss why he apparently does not resect some patients with peritoneal and hepatic metastases after exploration.

Finally I can suggest to Dr. Pearson that there is a way to avoid the liability of recurrent nerve problems, and that is to use the posterior approach, dissecting behind the sternomastoid and along the transverse processes of the cervical vertebrae to approach the esophagus. The nerve at risk with the posterior approach is, of course, the cervical symphathetic.

But a Horner's syndrome is less disabling than a vocal cord that will not work.

DR. RICHARD J. FINLEY (Closing discussion): One of the problems with transhiatal esophagogastrectomy for adenocarcinoma of the esophagogastric junction is the extent of the gastric resection. In this operation the lesser curve of the stomach is resected in continuity with the esophagogastric junction. In three of our patients there were tumors at the resection margins on final pathologic examination, which led to recurrent tumors at their anastomoses. Since that information has become available, frozen section examination of the gastric resection margin is performed at the time of surgery and if there is tumor at the resection margin a completion gastrectomy is carried out and swallowing is restored with a colon interposition. Colon interposition does have higher morbidity and mortality rates, but I believe it is justified to completely resect the cancer and restore swallowing.

Most of the patients who have recurrence of their tumors have extensive lymph node disease at the time of surgery. Previous reports of resection of gastric carcinoma suggest that most of the locally recurrent disease originates from lymph nodes metastasis. All the patients in our study who developed locally recurrent disease also had lymph node metastases at the time of original surgery. This suggests the need for adjuvant forms of therapy, such as radiotherapy, to reduce the recurrence from lymph node metastasis.

Many of the recurrent nerve palsies occurred early in my experience. I believe that this was due to the fact that we were putting a retractor in the tracheal esophageal groove in the neck. Furthermore if the vagus nerves are divided through the hiatus and above the tumor before pulling the esophagus into the abdomen, there is less chance of a traction injury of the left recurrent laryngeal nerve.

There is a high incidence of pulmonary emboli in this study. Since these emboli were documented, all the patients have received prophylactic heparin before and during their surgery.

Dr. Condon, I believe that patients with liver and peritoneal metastases from the adenocarcinoma of the esophagogastric junction have a very short life expectancy. Although transhiatal esophagogastrectomy offers excellent palliation with a short treatment time, these patients have been treated in our center with endoesophageal prosthesis to restore swallowing.

Experience with 647 Consecutive Tumors of the Duodenum, Ampulla, Head of the Pancreas, and Distal Common Bile Duct

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Between 1946 and 1987, 647 patients with periampullary tumors were diagnosed at the University of Chicago Medical Center. These included 549 tumors located in the head of the pancreas, 40 in the distal common bile duct, 29 in the duodenum, and 29 at the ampulla of Vater. Ninety-eight per cent of all tumors were adenocarcinoma, with 93% of the remaining being duodenal carcinoid or sarcoma. Operability rate ranged from 81% to 97%, according to the tumor location and histologic type. A combination of laparotomy, biopsy, and bypass was performed in 433 patients and only one survived 5 years (0.2%). Resectability rate ranged from 16.5% for pancreatic adenocarcinoma to 89.3% for ampullary tumors. Of the 133 resections, 80 were pancreatoduodenectomies, 29 total pancreatectomies, 7 duodenectomies, 2 gastrectomies, 8 common bile duct resections, and 7 local excisions. Overall 19% of patients who underwent radical resection died in the immediate postoperative period, although mortality has decreased to 5% since 1981. Mortality was 20% after a standard pancreatoduodenectomy and 24.1% after a total pancreatectomy. Five-year actuarial survival rates, including perioperative deaths, were 8.8%, 20%, and 32% for pancreatic, duodenal, and ampullary adenocarcinoma, respectively. One half of patients with sarcoma and two thirds with carcinoid of the duodenum survived 5 years. No patient with distal common bile duct adenocarcinoma achieved a 5-year survival rate. Multivariate analysis on all patients operated on ($n = 566$) revealed that the 5-year survival rate was significantly related to intent of operation (palliative 0.2%, curative 12%; $p < 0.001$), histologic type (adenocarcinoma 2%, carcinoid and sarcoma 31%; $p < 0.0001$), and site (ampullary and duodenal 21%, biliary and pancreatic 0.9%; $p < 0.001$). A second multivariate analysis, evaluating only those patients with adenocarcinoma who survived the perioperative period of the radical resection ($n = 97$) analyzed the influence of tumor size and differentiation, lymphatic, capillary, and perineural microinvasion, lymph node status, and type of procedure (pancreatoduodenectomy *vs.* total pancreatectomy) on 5-year survival. None of these additional variables was significantly associated with long-term survival rates. In addition we evaluated the presence of local or distant recurrence after resection by analyzing the findings from all autopsies performed on these patients ($n = 49$): 29.4% of patients died with local recurrence alone, 23.5% with distant recurrence alone, and 47.1% had both local and distant recurrences. The occurrence of multicentricity in pancreatic adenocarcinoma was investigated in 36 patients in whom the entire gland was examined histologically. Multicentricity was noted in only one instance (2.8%). These results suggest that intent of operation, tumor site, and histologic type determine the outcome of patients with periampullary tumors. Although a curative resection offers the best chance for long-term survival, our results emphasize the limitation of our staging and selection. Multicentricity occurs rarely and total pancreatectomy does not achieve a lower perioperative mortality or better survival rates than standard pancreatoduodenectomy, indicating that the latter is the resection of choice unless multicentricity is obvious at exploration.

ALLEN O. WHIPPLE SUCCESSFULLY performed and described a radical operation for the treatment of ampullary carcinomas in 1935.[1] Two years later, Alex Brunschwig[2] from the University of Chicago reported a patient with carcinoma of the head of the pancreas treated by a pancreatoduodenectomy. Since then this operation has been applied also to tumors of the duodenum and distal common bile duct. Today one half a century later, the debate still continues on the proper selection of patients for such radical procedure. In an effort to improve our ability to select the appropriate candidates for radical resection of tumors of the duodenum, ampulla, head of the pancreas, and distal bile duct, we analyzed our experience at the University of Chicago with such cancers. By using multivariate regression analysis, we tried to identify any significant clinical or pathologic variable that could be used to aid in this selection.

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Materials and Methods

Between 1946 and 1987, 647 patients with periampullary tumors were diagnosed at the University of Chicago Medical Center. These included 549 tumors located in the head of the pancreas, 40 in the distal common bile duct, 29 in the duodenum, and 29 at the ampulla of Vater. The clinical records of all of these patients were reviewed, and in all cases complete follow-up to December 1987 was obtained through our Registry of Neoplastic Diseases. Data on age, sex, race, tumor location, size, type of operation performed, and hospital deaths were specifically sought in each instance. Autopsy records, when available, were retrieved.

Histologic slides from all ampullary, duodenal, and biliary tumors and from resected pancreatic tumors were retrieved for determination of histologic tumor type, differentiation degree, vascular and/or lymphatic and/or perineural invasion by one pathologist (PJD) who was unaware of the patient's clinical course.

Long-term survival, using 5-year survival rate as the dependent variable, was analyzed by logistic regression analysis.[3] All patients who were operated on (n = 566) were analyzed. The following independent variables were entered into the multivariate analysis: age, sex, race, intent of operation (palliative *vs.* curative), histologic type (adenocarcinoma *vs.* carcinoid and sarcoma), and tumor location (ampullary and duodenal *vs.* biliary and pancreatic).

A second multivariate analysis evaluated only those patients with adenocarcinoma who survived a radical resection with curative intent (n = 97). Five-year survival was used again as the dependent variable, while the following independent variables were considered: tumor size, differentiation degree, presence of vascular and/or lymphatic and/or perineural invasion, lymph node status, and type of operative procedure used (pancreaticoduodenal resection *vs.* total pancreatectomy). Operative deaths were defined as those deaths occurring after operation in the hospital or within 30 days after discharge.

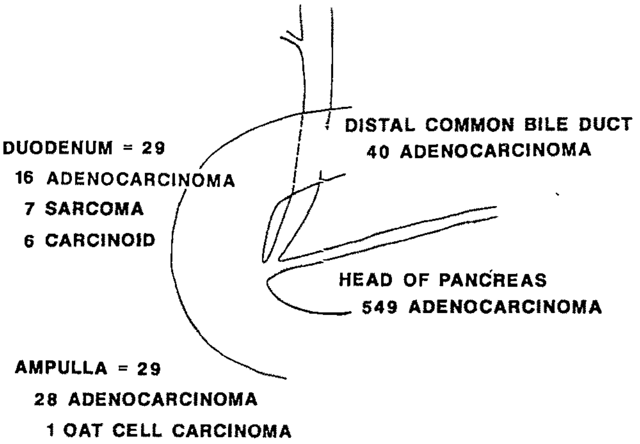

FIG. 1. Histology and location of 29 ampullary, 29 duodenal, 40 distal common bile duct, and 549 pancreatic tumors diagnosed at the University of Chicago Medical Center between 1946 and 1987.

TABLE 1. *Operability Rate*

Location	Histology	Operability Rate n (%)
Ampulla (n = 29)	Adenocarcinoma (n = 28) Oat cell carcinoma (n = 1)	28 (96.6)
Duodenum (n = 29)	Adenocarcinoma (n = 16)	13 (81.3)
	Carcinoid (n = 6)	5 (83.3)
	Sarcoma (n = 7)	6 (85.7)
Distal common bile duct (n = 40)	Adenocarcinoma (n = 40)	36 (90)
Head of pancreas (n = 549)	Adenocarcinoma (n = 549)	478 (87)

Results

Figure 1 summarizes the histology and the location of the 647 tumors. As expected most of the tumors were found in the head of the pancreas (85%), and almost all were adenocarcinomas (98%). Only in the duodenum was there a substantial likelihood (almost 50%) that the tumor would be another cell type: 6 of 29 were carcinoids and 7 of 29 were sarcomas.

The operability rates, as outlined in Table 1, depended largely on location, with the highest rate of 97% found for patients with tumors of the ampulla and the lowest rates of 81% to 86% associated with tumors of the duodenum. Eighty-one patients did not undergo any operative procedure.

Of the 566 patients operated on, 433 underwent nonresectional treatment. Table 2 summarizes the rate of nonresectional treatment, its associated hospital mortality and 5-year survival, classified by location and histology. The rate of nonresectional surgical treatment varied dramatically depending on the tumor site. Only 11% of patients with ampullary adenocarcinoma underwent nonresectional treatment, compared to 84% of patients with adenocarcinoma in the head of the pancreas. The outcome was uniformly poor with a high postoperative mortality rate and only one 5-year survivor.

The primary tumor was resected in the remaining 133 patients, 84 men and 49 women. The mean age at the time of operation was 60.5 years, with a range from 10 to 85 years. Ninety-six patients were white and 37 were black. Table 3 summarizes the demographic characteristics by tumor site.

Of the 133 patients whose tumors were resected, 126 (95%) patients underwent a radical resection of the tumor, and seven patients had a local excision. The majority of

TABLE 2. *Nonresectional Treatment*

Location	Histology	n and % of All Patients with Same Tumor Type		Hospital Mortality n (%)	5-Year Survival n (%)
Ampulla	Adenocarcinoma	3	10.7	2 (67)	0 (0)
Duodenum	Adenocarcinoma	3	23.1	0 (0)	0 (0)
	Carcinoid	1	20	0 (0)	0 (0)
	Sarcoma	1	16.7	0 (0)	0 (0)
Distal common bile duct	Adenocarcinoma	26	72.2	5 (19.2)	0 (0)
Head of pancreas	Adenocarcinoma	399	83.5	53 (14.3)	1 (0.2)
Total		433			

radical resections performed were pancreaticoduodenectomies (n = 80) and total pancreatectomies (n = 29). Table 4 details the resectability rate and the procedure according to the location and the histology of the primary tumor for all 133 patients.

Nineteen per cent (n = 24) of the 126 patients who underwent a radical resection died during the immediate postoperative period, although only one of 20 patients resected since 1981 died in the postoperative period, yielding a recent mortality rate of 5%. Overall, mortality was 20% after a standard pancreatoduodenectomy and 24.1% after a total pancreatectomy; none of the patients with local resections died after operation. Long-term survival was improved by radical resection as compared to nonresectional procedures. Nineteen of 126 patients who had radical resections were alive at follow-up and 14 patients (11%) were alive at least 5 years after operation; only one of the nonresected patients survived 5 years. Of the seven patients with local resection, four were alive at follow-up and of those, two were alive 5 years after operation. Table 5 delineates the hospital mortality and the long-term survival rates, classified by the extent of operation performed and by the location and histology of the primary tumor for all 133 patients.

A multivariate logistic regression analysis was performed to evaluate statistically significant relationships between clinical and pathologic features and patient survival in the group of 566 patients who underwent an operation. Only three independent variables, intent of operation, histologic type, and site were found to correlate significantly with 5-year survival (Fig. 2). As observed above, patients undergoing a curative operation had a significantly improved 5-year survival rate compared to patients undergoing palliative surgery (16 of 33 patients = 12% *vs.* 1 of 433 patients = 0.2%, respectively; $p < 0.001$). In addition there was a significantly increased ($p < 0.001$) rate of survival for patients with tumors of the ampulla or duodenum as compared to patients with tumors of the bile duct or head of the pancreas (12 of 52 patients = 21% *vs.* 5 of 514 patients = 0.9%, respectively). The few patients with carcinoids or sarcomas fared significantly better than did patients with adenocarcinomas (4 of 11 patients = 31% *vs.* 13 of 555 patients = 2%, respectively; $p < 0.0001$).

The second multivariate analysis, evaluating only those 97 patients with adenocarcinoma who survived the perioperative period after a radical resection, analyzed the influence of other pathologic characteristics on long-term survival. Data for these variables were not available for all patients and are summarized in Table 6. The multivariate analysis showed that none of these additional variables influenced long-term survival.

To present our results in a clinically useful manner, survival rates based on life table analysis were calculated. Figure 3 displays the differences among histologic types of duodenal tumors in 5- to 10-year survival rates after

TABLE 3. *Age, Sex, and Race of Patients with Resected Tumors*

		Age			Sex		Race	
Tumor Type	n	Mean	Min	Max	M	F	White	Black
All Patients	133	60.5	10	85	84	49	96	37
Ampulla	25	60.1	43	76	14	11	23	2
Pancreas	79	60.7	31	83	51	28	56	23
Duodenal adenocarcinoma	10	62.8	49	72	6	4	5	5
Duodenal carcinoid	4	52.7	44	65	3	1	1	3
Duodenal sarcomas	5	54.7	10	85	3	2	3	2
Distal common bile duct	10	64.8	47	74	7	3	8	2

TABLE 4. *Type of Procedure for Resected Tumors*

Location	Resectability Rate n (%)	Radical Resections: Pancreatico-duodenectomy	Radical Resections: Total Pancreatectomy	Radical Resections: Duodenal Resection	Radical Resections: Gastrectomy	Radical Resections: CBD resection	Local Excisions
Ampulla	25 (89.3)	20	3	—	—	—	2
Duodenal adenocarcinoma	10 (76.9)	5	—	5	—	—	—
Duodenal carcinoid	4 (80)	1	—	1	1	—	1
Duodenal sarcoma	5 (83.3)	—	—	1	1	—	3
Distal common bile duct	10 (27.8)	1	—	—	—	8	1
Pancreas	79 (16.5)	53	26	—	—	—	—
Total	133	80	29	7	2	8	7

radical resections. Patients with duodenal adenocarcinoma had a poorer long-term prognosis than patients with carcinoids or sarcomas.

Figure 4 compares the 5-to 10-year survival rates by tumor site for all four periampullary sites. Patients with ampullary and duodenal tumors fared better after a curative resection than patients with tumors in the head of the pancreas or distal common bile duct. Five-year actuarial survival rates, including perioperative deaths, were 8.8%, 20%, and 32% for pancreatic, duodenal, and ampullary adenocarcinoma, respectively. No patient with distal common bile duct adenocarcinoma achieved a 5-year survival. Of note, one patient with ampullary and two patients with pancreatic adenocarcinoma died of recurrent disease between 5 and 10 years after their curative procedure.

The development of local or distant recurrence after resection was analyzed by reviewing available autopsy findings. Of 49 autopsies, 15 were performed on patients who had not undergone resection. Of the remaining 34 autopsies, 19 were performed on patients with pancreatic adenocarcinomas, 2 with biliary carcinomas, 7 with ampullary, and 6 with duodenal carcinomas (see Table 7). Sixteen autopsies were performed in the immediate postoperative period and metastatic tumor was found in only one instance. The remaining 18 autopsies were performed after a mean survival of 9.1 months (range, 2 to 28.3 months). Ten autopsies followed resection of a pancreatic cancer and eight followed resection of an ampullary or duodenal cancer. One patient with pancreatic cancer died 86 days after operation from massive hemorrhage due to a marginal ulcer and no tumor was found at autopsy. In the remaining 17 patients, 29.4% had only local recurrence, 23.5% had only distant disease, and 47.1% had both local and distant recurrences.

The question of multicentricity in pancreatic adenocarcinoma was investigated in 36 patients in whom the entire gland was examined histologically (Table 8). In one patient (2.8%), multicentricity was evident at operation and the patient underwent a total pancreatectomy. In 25 additional patients treated by a total pancreatectomy, no evidence of multicentricity was found on histologic examination of the resected specimen. In the remaining ten patients who initially underwent a Whipple procedure and later an autopsy, histologic examination of the entire gland failed to show any evidence of multicentricity.

TABLE 5. *Resectability and Hospital Mortality Rates*

Location	Histology	Radical Resections: Total (n)	Radical Resections: Hospital Mortality (n) (%)	Radical Resections: 5-Year Survivors	Radical Resections: Alive with F/U < 5 yrs.	Local Resections: Total (n)	Local Resections: Hospital Mortality (n)	Local Resections: 5-Year Survivors	Local Resections: Alive with F/U < 5 yrs.
Ampulla	Adenocarcinoma	23	5 (22)	6	1	1	0	1	0
	Oat cell carcinoma	—	—	—	—	1	0	0	0
Duodenum	Adenocarcinoma	10	1 (10)	1	1	—	—	—	—
	Carcinoid	3	0	2	0	1	0	0	0
	Sarcoma	2	0	1	0	3	0	1	2
Distal common bile duct	Adenocarcinoma	9	2 (22)	0	0	1	0	0	0
Head of pancreas	Adenocarcinoma	79	16 (20)	4	3	—	—	—	—
Total		126	24 (19)	14	5	7	0	2	2

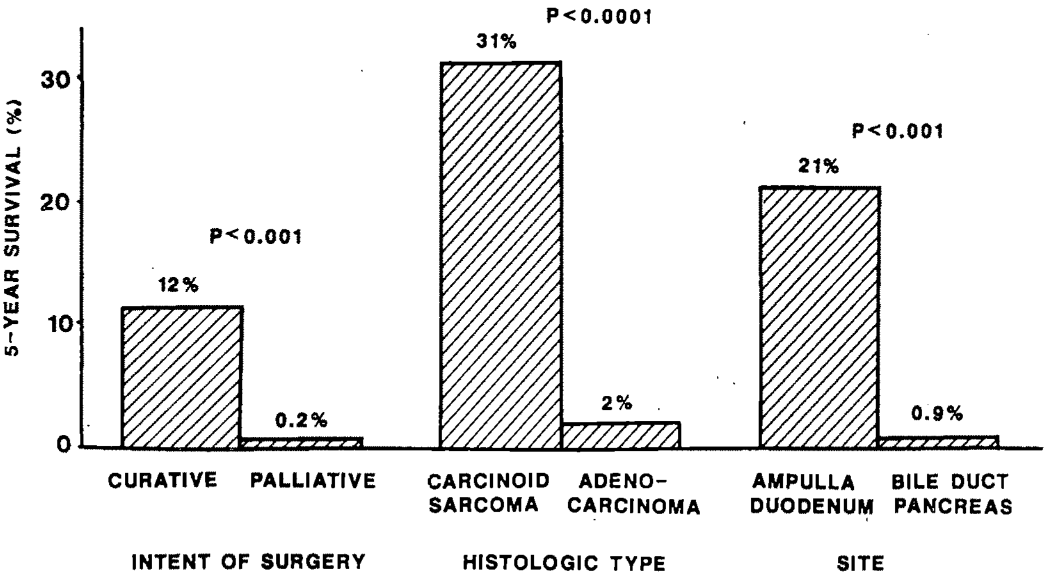

FIG. 2. Factors influencing 5-year survival in tumors of the ampulla, duodenum, distal common bile duct, and head of the pancreas.

Discussion

The results of our analysis of the 647 patients with periampullary tumors diagnosed at our institution during the past 40 years indicate that outcome depends largely on the site of the tumor, its histology, and its resectability. The prognosis for long-term survival was significantly better for patients with cancer of the duodenum and ampulla and worse for those with cancer of the pancreas and common bile duct.

With the exception of one oat cell carcinoma of the ampulla, all tumors outside of the duodenum were adenocarcinomas. In patients with tumors of the duodenum, almost 50% were another cell type. Although the nonadenocarcinomas were few in number (n = 14), cell type significantly influenced outcome: patients with carcinoids or sarcomas fared significantly better than patients with adenocarcinomas.

We determined that once the diagnosis was made, patients whose tumors were resected had significantly better

TABLE 6. *Clinicopathologic Characteristics of Resected Tumors in Patients Surviving the Perioperative Period*

Size (n = 78 cm)			Mean		Min		Max
Ampullary (18)			1.77		0.3		5.5
Pancreatic (47)			3.71		0.8		9.0
Duodenal (7)			5.6		3.0		11.0
Distal common bile duct (6)			2.2		1.0		3.7
Differentiation Degree (n = 85)			Well		Moderate		Poor
Ampullary (18)			15		2		1
Pancreatic (50)			19		22		9
Duodenal (10)			5		3		2
Distal common bile duct (7)			4		2		1
	Lymphatic (n = 68)		Perineural (n = 65)		Capillary (n = 45)		No Invasion
Invasion (n)	+	−	+	−	+	−	
Ampullary (18)	15	3	12	6	2	16	3
Pancreas (50)	27	6	25	5	9	6	2
Duodenal (10)	6	4	2	8	2	7	3
Common bile duct (7)	5	2	1	6	1	2	1
Lymph Node Status (n = 86)			positive		negative		
Ampullary (18)			9		9		
Pancreatic (54)			31		23		
Duodenal (10)			3		7		
Distal common bile duct (4)			1		3		

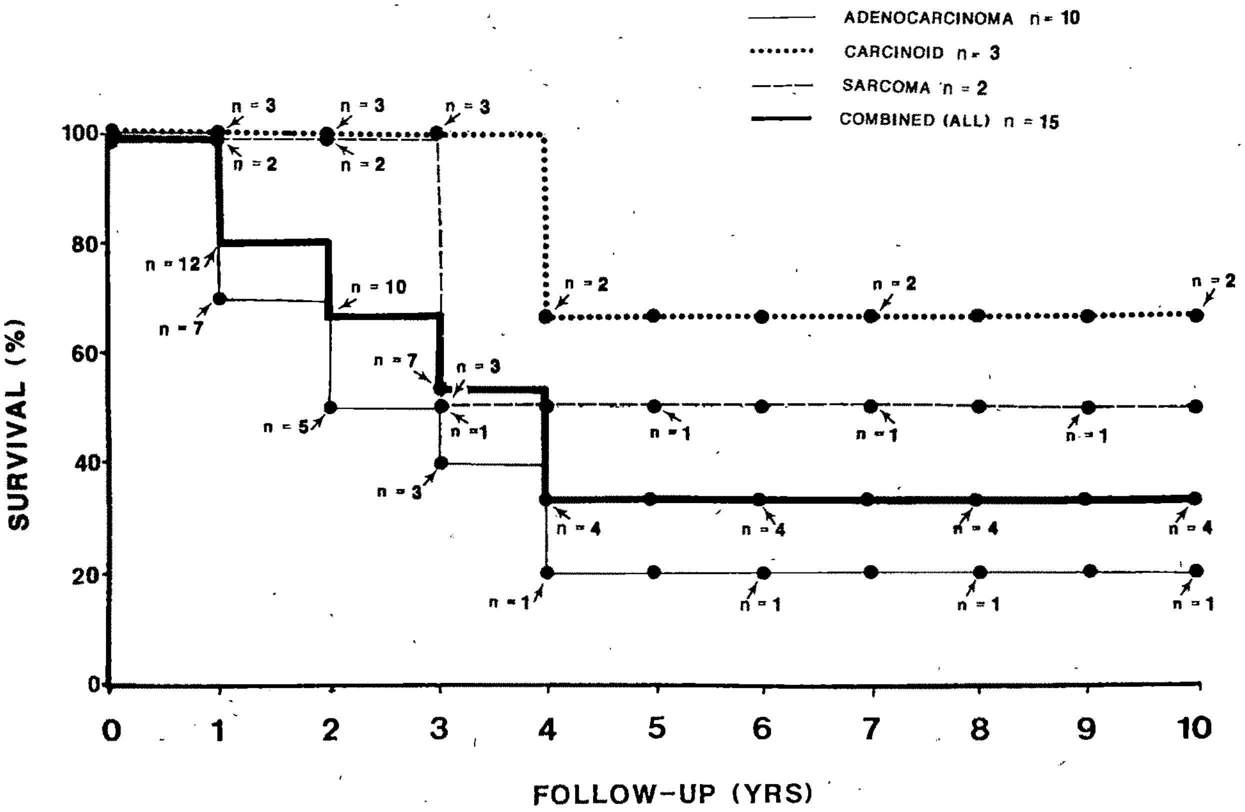

FIG. 3. Long-term survival rates in patients after radical resection of a duodenal tumor. Patients who died of intercurrent disease were censored at the time of the last known follow-up.

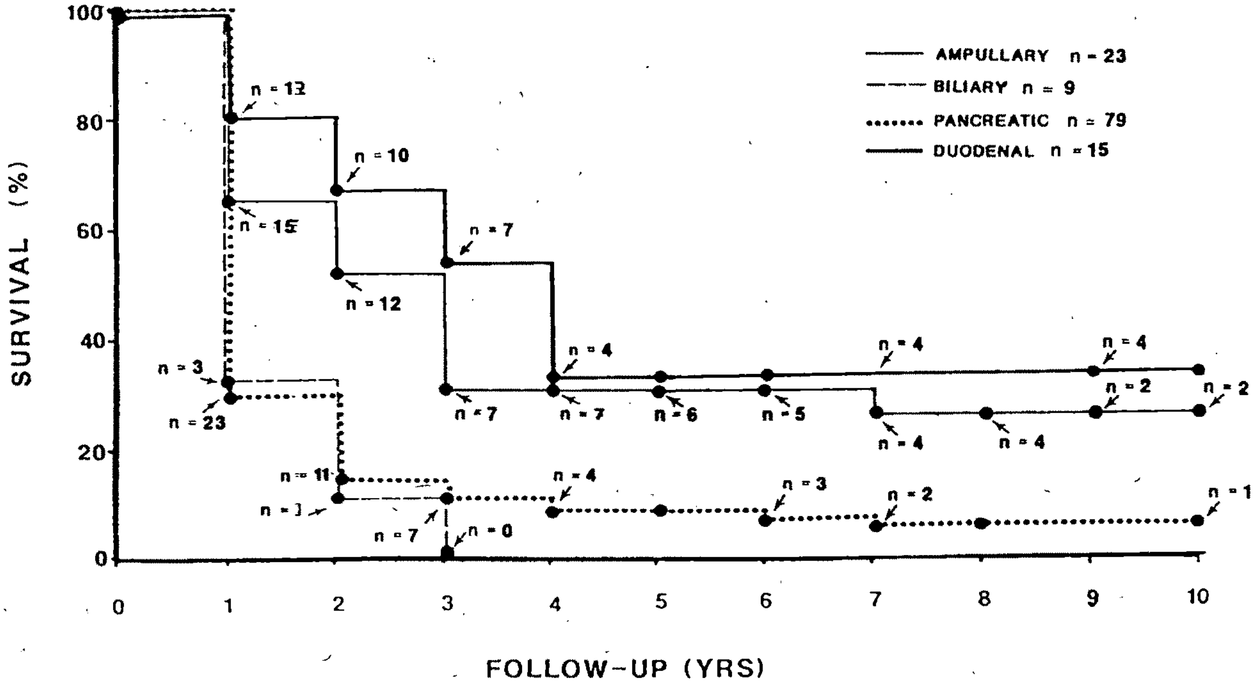

FIG. 4. Long-term survival in patients after radical resection of a tumor of the ampulla, duodenum, distal common bile duct, and head of the pancreas. Patients who died of intercurrent disease were censored at the time of the last known follow-up.

TABLE 7. *Autopsy Findings After Resection*

		Late Deaths			
Tumor Site	Perioperative Deaths	No Recurrence	Distant	Local	Distant and Local
Pancreas (n = 19)	9	1	1	3	5
Ampulla (n = 7)	4	—	2	—	1
Duodenum (n = 6)	1	—	1	2	2
Common bile duct (n = 2)	2	—	—	—	—

prognoses than patients who underwent palliative operations. Although the site of the tumor influenced resectability rates, using a multivariate analysis, our results suggested that the type of operation performed (resection or palliation) significantly influenced outcome for all sites.

Our results are consistent with other series reported in the literature. Table 9[4-9] outlines the distribution by site of resectable periampullary tumors described in the literature during the past decade. Although our series included a higher percentage of resected pancreatic tumors (61%), the differences were not large and our distribution was quite similar to that reported by Grace in 1986.[8]

When the operability and 5-year survival rates were compared to other series reported by site of tumor, our results were similar. Table 10[10-46] details the operability, resectability, operative mortality, and 5-year survival rates of patients with adenocarcinoma of the head of the pancreas extracted from reports in which such information was specifically stated. These series varied in the number of patients analyzed, from 27 patients to 1819. Operative mortality rates ranged from a low of 0% to a high of 64%, while 5-year survival was uniformly poor, varying from 0% to 17%. Regardless of the number of patients followed, no series reported more than five[40] patients surviving for 5 years. We averaged the results reported in the literature and found that our figures were comparable: the averaged operative mortality rate was 21% compared to ours of 19%, while the averaged crude 5-year survival was 2.4% compared to ours of 5%.

Carcinoma of the extrahepatic bile duct is located in the distal common bile duct in approximately one third of instances. Because our 40 cases were limited to the distal common bile duct, we compared the results with other similarly defined series reported in the literature during the past decade (see Table 11)[47-53]. Because the tumor is uncommon, most series, including our own, report on a small number (ranging from five to 15) of patients undergoing resection; we report on ten. Because of the small numbers, there is wide variability in the resectability, operative mortality, and 5-year survival rates. Our findings are consistent with those reported, although the 5-year survival rate for our patients is one of the lowest: none of the ten patients survived. Although most of the other series reported a better long-term outcome, few patients survived. Including our series in an averaged 5-year survival, only 17.5% of patients survived 5 years.

Tables 12[54] and 13[55-57] summarize similar results reported in the literature for adenocarcinomas of the ampulla and of the duodenum. Our results are consistent with these reports, but as noted with common bile duct tumors, the numbers from the series are very small, and so there is a marked variability in operative mortality and 5-year survival.

Of our 433 patients with periampullary tumors who did not undergo a resectional procedure, only one survived 5 years. This finding is also consistent with other reported cases of histologically proved adenocarcinoma of the pancreas having a long-term survival in the absence of radical resection. Gudjonsson,[46] in an extensive review of the world literature, found 12 5-year survivors among 33,000 unresected patients (0.04%). The unexpected nature of these findings suggests that, although pancreatic adenocarcinoma is a very aggressive tumor with a hopeless prognosis when unresected, on rare occasions, its behavior may be unpredictable.

Of the 133 patients who underwent resection, seven had a local excision. With the exception of one bile duct tumor, local excision was performed only in ampullary (n = 2) and duodenal (n = 4) cancers. At follow-up four patients were alive and of those, two were alive 5 years after operation. The limited number of local excisions does not allow us to comment on the validity and indications for such approach. The first reported local excision of an ampullary lesion is attributed to Halstead in 1898.[58] Recently several authors have reported their experience with local excisions and their 5-year survival rates have ranged from 17% to 41%.[7,9,59-61] Tarazi[9] reported on 11 adenocarcinomas of the ampulla of Vater treated by local

TABLE 8. *Multicentricity in Pancreatic Adenocarcinoma: Data from Clinical and Histologic Observations*

	Multicentricity		
Procedure (N = 36)	Exploration	Histologic Examination of Specimen	Autopsy
Total Pancreatectomy (n = 26)	one*	one*	—
Whipple Procedure (n = 10)		None	
5 Postoperative deaths			None
5 Survivors (2 to 28 months)			None

* Same case.

TABLE 9. *Per cent Distribution of Resected Pancreatic, Ampullary, Duodenal, and Distal Biliary Adenocarcinoma in Recent Representative Series*

		Pancreatic		Ampullary		Duodenal		Distal CBD	
Author		n	%	n	%	n	%	n	%
Cohen[4]	1982	36	42.3	22	25.9	16	18.8	11	12.9
Herter[5]	1982	75	52.1	44	30.6	15	10.4	10	6.9
Kellum[6]	1983	18	46.7	17	37.8	3	8.9	3	6.6
Jones[7]	1985	34	34.7	40	40.8	12	12.2	12	12.2
Grace[8]	1986	37	56.9	18	27.7	5	7.7	5	7.7
Tarazi[9]	1986	26	26.0	45	46.0	17	17.0	11	11.0
Michelassi	1989	79	61.2	25	20.9	10	10.1	10	7.7

resection; three patients later required another excision for a local recurrence and one patient underwent a total of three local re-excisions and eventually died of systemic disease 2 years later. Local excision, therefore, although associated with a low perioperative mortality rate, appears to have a high local recurrence rate. In addition its long-term therapeutic value is questionable if a disappointingly low 17% to 41% 5-year survival rate is achieved when

TABLE 10. *Operability, Resectability, Mortality, and Crude 5-Year Survival Rates in Adenocarcinoma of the Head of the Pancreas*

Author/Year		Patients	Operability Rate		Resectability Rate		Operative	5-Year Survival	
		n	n	%	n	%	Mortality %	n	%
Broadbent[10]	1951	72	66	92	7	11	NA	NA	NA
Brintnall[11]	1952	67	58	87	15	26	13	NA	NA
Cliffton[12]	1952	122	89	73	12	13	33	2	16.7
McDermott[13]	1953	112	75	67	0	0	NA	0	0
		136	100	74	33	33	33	0	0
Stafford[14]	1954	37	37	100	11	30	27	0	0
Gullick[15]	1959	65	49	75	7	14	64	0	0
Dancer[16]	1965	28	23	82	6	26	0	1	16.7
Halbert[17]	1965	74	46	62	13	28	30.7	0	0
Collins[18]	1966	67	57	85	11	19	18	0	0
Morris[19]	1966	121	109	90	26	24	38.5	2	7.7
Salmon[20]	1966	203	163	80	38	23	33.3	1	2.6
Rastogi[21]	1967	49	42	86	2	5	NA	0	0
Richard[22]	1969	190	163	86	45	28	NA	2	4.4
Vijayanager[23]	1970	61	49	80	NA	NA	NA	NA	NA
Pope[24]	1971	114	104	91	10	10	20	0	0
Elmslie[25]	1972	27	26	96	NA	NA	NA	NA	NA
Parkash[26]	1972	48	41	85	0	0	NA	0	0
Richards[27]	1973	152	136	89	27	20	15	0	0
Douglass[28]	1974	81	59	73	10	17	25	1	10
Hertzberg[29]	1974	193	181	94	12	7	13	0	0
Wilson[30]	1974	103	93	89	13	14	23	0	0
Shapiro[31]	1975	297	162	55	24	15	8	0	0
Webster[32]	1975	75	58	77	8	14	38	0	0
Balasegaram[33]	1976	66	64	97	7	11	43	0	0
Hines[34]	1976	115	108	94	22	20	7	0	0
Nakase[35]	1977	1819	1635	90	322	20	25.3	0	0
Sato[36]	1977	95	82	85	22	27	14	2	9.1
Stephenson[37]	1977	222	192	86	35	18	17	NA	NA
Bergstrand[38]	1978	271	238	88	34	14	25	0	0
Bungay[39]	1980	56	47	84	NA	NA	NA	NA	NA
Bjorck[40]	1981	480	NA	NA	62	13	10	5	8.1
Deschamps[41]	1984	106	75	71	15	20	20	0	0
Rosenberg[42]	1985	461	365	79	24	7	9	3	12.5
Parker[43]	1985	142	120	85	10	8	20	0	0
Matsuno[44]	1986	172	164	96	38	23	12.7	2	5.3
Ubhi[45]	1986	98	83	85	1	1	NA	0	0
Gudjonsson[46]	1987	196	165	84	8	5	0	1	12.5
Total		6793	5323	78	930	17.5	21	22	2.4
Michelassi	1989	549	478	87	79	16.5	20	4	5.0

TABLE 11. *Percentage of Extrahepatic Biliary Tumors in Distal Portion of the Common Bile Duct, Resectability Rate, Operative Mortality, and Crude 5-Year Survival Rate in Representative Series Published in the Last Decade*

Author	% of Extrahepatic Biliary Tumors in Distal CBD	Resectability Rate n	Resectability Rate %	Operative Mortality %	5-Yr. Survival n	5-Yr. Survival %
Lees[47] 1980	40.5	6	19	0	1	16.7
Takasan[48] 1980	40	15	75	33	3	16
Rodgers[49] 1981	69.5	6	12.5	—	0	0
Tompkins[50] 1981	19	12	67	8	3	25
Alexander[51] 1984	13	14	100	21	2	14
Langer[52] 1984	23	12	47	—	4	33
Adkins[53] 1986	18	5	50	—	1	20
Michelassi 1989	NA	10	25	10	0	0
Total		80		—	14	17.5

only the most favorable, potentially curable lesions are selected as reported above.[7,9,59–61]

The primary purpose of this study was to identify clinical or pathologic characteristics that might predict long-term prognosis in patients with periampullary tumors. Because the operability and survival characteristics of our cohort of patients are similar to those reported by others, the results of our multivariate analysis should be relevant for others as well.

The principal findings from the multivariate analysis were previously summarized: only site, histology, and resectability were significantly associated with long-term survival. Other clinical and pathologic characteristics, including the type of resection, status of regional lymph nodes, degree of differentiation, invasiveness of the tumor and its size, were not predictive of high-risk or low-risk patients. Many other series have demonstrated this lack of clinically useful identifying characteristics. For example survival in node- positive patients is essentially similar to that of node-negative patients, an observation also noted by others.[62,63]

TABLE 12. *Resectability Rate, Operative Mortality, and Crude 5-Year Survival Rate for Ampullary Adenocarcinoma in Recent Representative Series*

Author	Resectability Rate n	Resectability Rate %	Operative Mortality n	Operative Mortality %	5-Yr. Survival n	5-Yr. Survival %
Cohen[4] 1982	22	—	—	23.8	—	30.0
Herter[5] 1982	44	—	—	—	10	22.7
Kellum[6] 1983	17	—	2	11.8	—	50.0
Jones[7] 1985	36	100	—	—	13	32.0
Tarazi[8] 1986	46	—	6	13.0	—	37.2
Hayes[54] 1987	31	88	8	25.8	12	38.7
Michelassi 1989	25	89.3	5	20	6	24.0

TABLE 13. *Resectability Rate, Operative Mortality, and Crude 5-Year Survival Rate for Duodenal Adenocarcinomas in Representative Series*

Author	Resectability Rate n	Resectability Rate %	Operative Mortality n	Operative Mortality %	5-Yr. Survival n	5-Yr. Survival %
Crane[55] 1973	6	100	4	67	1	16.7
Alwmark[56] 1980	32	65.3	7	21.9	9	28.1
Joesting[57] 1981	—	—	12	11.6	21	35.6
Michelassi 1989	10	76.9	1	10	1	10

These results are not surprising. Pancreatic adenocarcinomas are known for their aggressive course. The retroperitoneal location provides little margin for growth before invasion occurs. The proximity of the portal vein, hepatic and superior mesenteric arteries may preclude removal of the tumor even in its early stages. Moreover the location of the pancreas at an anatomic water-shed with drainage to multiple lymph node basins invites early and widespread dissemination of tumor and makes a curable lesion an uncommon event. Conversely ampullary tumors have been long recognized to have a better prognosis.

In agreement with our results, several authors have shown that resection is associated with longer survival than bypass or biopsy only. The better prognosis of patients who undergo tumor resection compared to those who undergo palliative therapy could be due to a selection of patients with earlier disease. This argument could support the thesis that pancreatoduodenectomy has not proved successful and should not be used in the treatment of cancer of the head of the pancreas. However because the prognosis and quality of life for nonresected tumors is so poor, and resectional therapy is the only potentially curative procedure, we favor selected resections in the presence of the low postoperative mortality rates achieved in these recent years.

Another argument in favor of surgical resection is that it is sometimes difficult to differentiate between tumors of the ampulla, duodenum, and lower third common bile duct and tumors arising from the pancreas. An aggressive approach in these doubtful cases is justifiable because of the better long-term prognosis of duodenal and ampullary cancers.

Total pancreatectomy has been advocated because of fear of pancreatic cancer multicentricity, spillage of neoplastic cells along the pancreatic duct with implantation in the body and tail of the pancreas, fear of margin involvement by tumor, and the avoidance of the pancreaticojejunal anastomosis. However our data indicate that perioperative mortality was comparable for both procedures and multivariate analysis showed no significant difference in long-term survival after a standard pancreaticoduodenectomy or a total pancreatectomy.

Our analysis also does not justify performance of total pancreatectomy on the basis of multicentricity. We found multicentricity evident at exploratory laparotomy in only one patient. In the other 35 cases, in which the whole gland was eventually examined histologically, no evidence of multicentricity was found. These cases included ten patients who initially underwent a Whipple procedure and a later autopsy. Herter[5] found similar results: one case of multicentricity and two cases of cellular atypia in the tail of the pancreas among 42 total pancreatectomy specimens. In contrast Tryka and Brooks[64] analyzed specimens from 25 patients undergoing a total pancreatectomy for adenocarcinoma of the head of the pancreas and found that in 38% there was tumor spread beyond the local palpable tumor mass. Ross[65] in 1954 described multicentricity in one of his four patients undergoing total pancreatectomy, and Ihse,[66] Levin,[67] Pliam,[68] and Edis[62] reported multicentricity rates varying between 17% and 32%. Although we cannot explain the differences in the incidence of multicentricity reported, considering the increased postoperative morbidity associated with a total pancreatectomy, the similar perioperative mortality and the comparable long-term survival rates between total pancreatectomies and pancreatoduodenectomies, we would recommend a Whipple procedure unless multicentricity is obvious at exploration.

In conclusion, our results suggest that intent of operation, site, and histologic type determine the outcome of patients with periampullary cancers. Although a curative resection offers the best chance for long-term survival, our results emphasize the limitation of our ability to stage and select. Unless multicentricity is documented during exploration, a pancreatoduodenectomy is the resection of choice.

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DISCUSSION

PROFESSOR M. TREDE (Mannheim, Germany): I thank you very much for this chance to compliment Dr. Michelassi and Dr. George Block and his group from Chicago for this presentation. It is an excellent, very clear, very honest albeit dismal picture that they have painted. But as their experience spans 41 years, I wonder if this is the whole true story as of today in 1989. If it were, that would be water on the mills of the pessimists who question the cost-effectiveness of this surgery and of those who, perhaps with tongue in cheek, are suggesting that "Congress pass a law making it illegal to do a Whipple operation." Sometimes I think the history of pancreatic resection is a bit like climbing Everest. It took more than 30 years and many costly expeditions to put two men on the summit. Today, on a fine day, 12 at a time will make it, including 60-year olds (and even women!) and no one really knows the reason. The equipment has improved a little. I don't think the men are really any better. It is as though a spell has been broken, and so our more recent experience in Mannheim makes us cautiously optimistic.

Looking at the late results, we can plot the survival curve of 106 patients whose true ductal adenocarcinoma of the pancreas was resected, according to Kaplan-Meier. All patients are included here, whether the resection was partial or total, and whether they survived the operation (and 2 of these 106 did not). This curve crosses the magic 5-year limit at 37%.

Now you may not trust "actuarial survival," and I think you would probably be right. So let us drop all statistical gimmicks and just look at the fate of those 50 patients whose resection for adenocarcinoma of the pancreas, be it partial or total, took place more than 5 years ago before October 1983; (Slide) you can see that 41 have died since. But nine patients are still alive, which is a 5-year survival rate of 18%. For papillary carcinoma, by the way, it amounts to 47%. I hasten to add that the histologies of these nine survivors were reviewed by two independent pathologists, and they were confirmed. But I must also admit that 2 of these 9 patients have died after crossing the 5-year line. And it is a sobering thought that these two died of late recurrent pancreatic cancer.

That brings me to my two questions. First have you considered adding some adjuvant radio- and chemotherapy to your surgery? Second if you break up your 40-year experience into time periods, have you not seen some improvement in the last decade with surgery alone?

DR. JOHN W. BRAASCH (Boston, Massachusetts): We noted yesterday after Dr. Moore's superb discussion of Dr. Starzl's paper a complete lack of other discussants, and I must say I felt the same pangs in following Professor Trede this morning.

We have just heard a monumental 40-year experience on the surgical treatment of periampullary malignancy with a multivariant analysis of prognostic factors. I must say that this is the bad news of this subject, but let us try to find the good news. My remarks will be based on experience in the last 10 years with about 110 pylorus- preserving resections for periampullary neoplasma. We, like the authors in their last 10 years, have experienced a mortality rate of 5% or less, and this is fairly common around the world in places of experience. We agree that tumor site, intent of operation, and the histology of the tumor are the primary factors in influencing the result. A few other factors, such as nodes and lesion size, may influence the intent of the operation and thus have a secondary effect.

Our survivorship is somewhat more optimistic. For instance, 5-year ampullary carcinoma survival is about 45%. As has been stated, we take a rather uncertain view of the Kaplan-Meier curves, and this 45% is an estimation of what survival will be like in another year or so. Our duodenal survival will be about 50%, distal bile duct 35% to 40% and head of the pancreas lesions will be about 15% to 20%.

This little better news is explainable by several possibilities. It is possible that our patients get to us earlier, more arrive with the least promising cases screened out, and last, our criteria for resectability of pancreatic head tumors are fairly rigorous. For instance, patients who have back pain preceding jaundice are seldom resected. Patients with extension of the tumor toward the hepatic artery or superior mesenteric vessels are not resected, and the same can be said for positive aortic nodes or nodes along the hepatic and mesenteric arteries. From another standpoint, CT scanning and ERCP are very helpful in more accurate recognition of the site of origin of the tumor. So the fear of missing the resection of a favorable ampullary tumor, for instance, does not lead to the resection of many unfavorable cancers of the pancreas instead.

DR. CHARLES FREY (Sacramento, California:) Dr. Michelassi and his co-authors have presented us with a well-studied group of patients with malignant tumors of the head of the pancreas, duodenum, distal common bile duct, and ampulla. I agree with the other discussants that the operative mortality and the resectability rates that the authors report are related to the length of the study.

I have a number of questions for the authors. Could they tell us, based on their recent experience, if they have been able to increase the resectability rate of their cancers of the head of the pancreas, and if so, to what degree? Also, could the authors tell us why cancer of the head of the pancreas was included under the heading of periampullary cancer, and why, if sarcomas and carcinoids were included in their report, they excluded malignant islet cell tumors of the head of the pancreas?

Did the low incidence of multicentric tumors that they report have anything to do with the fact that they were looking only at patients with cancer of the head of the pancreas?

Two years ago they reported on 199 patients with cancer of the pancreas. Did these other patients with pancreatic cancer have a higher incidence of multicentric tumors?

DR. JOHN PETER MINTON (Columbus, Ohio): I wish to compliment the authors of the 40-year summary of 647 periampullary tumors. The most striking finding that I noticed was a significant decrease in the hospital mortality rates associated with the Whipple procedure since 1981. I would like you to comment on any technical or other changes that may have occurred since that time so we might all benefit.

I also noted a distinct tendency toward the Whipple prodedure as the operation of choice, and I would like you to comment or clarify the reasons why total pancreatectomy has slipped into the background of your surgical armamentarium.

Finally I note that the 647 patients during a 40-year period represent about 16 new patients in that institution per year, and I think that a comment about how your hospital administrators are dealing with the DRGs in these situations would be appropriate.

DR. LOREN J. HUMPHREY (Kansas City, Kansas): This important paper is timely for an era of decreasing mortality rates with the Whipple procedure. It has shown succinctly those variables that should encourage the surgeon to select the procedure with enthusiasm.

I rise to make two points.

With permission of the authors, P W. Humphrey from the University of Illinois Medical School in Peoria, P. A. Humphrey from the pathology department at Duke, and Dr. Stuarts Roberts, a senior member of this Association, I would like to bring to the audience the indication of the Whipple procedure for another histologic type, that should prompt the surgeon to be enthusiastic about performing a Whipple procedure.

Intrigued by a patient operated on by Dr. Roberts, the authors reviewed the world literature on intestinal lymphoma. As you can see, lymphomas comprise 1% of gastrointestinal malignancies, and 3.5% of these are duodenal in location, so it is no wonder with the rarity that the authors did not have such a primary of the duodenum.

Roberts et al. found that there were 104 duodenal lymphomas that were mentioned or referred to in various studies, but only 16 were documented sufficiently in detail to make the diagnosis with certainty.

Their case, number 17, brought forth the usual data that you can see in the 16 cases. The average patient age was 45 years and they described the diagnostic problems that one entertains when a biopsy indicates duodenal lymphoma and that is pseudolymphoma *versus* a true lymphoma of the duodenum. The average survival of those 16 patients was 9.1 months.

Case 17 that Dr. Roberts operated on, I think, brings forth the point that with today's technology with immunocytopathology the diagnosis is relatively easy. These tumors are diagnosed early thanks to endoscopic techniques, so that the resectability, which in duodenal lymphoma was very small compared to pancreatic cancer, should now be quite high.

The second point I wish to make with certain glee because I was the 17th case that Dr. Roberts and his colleagues reported, and that was more than 2 years ago. The tumor was a B cell lymphoma of the small cleave cell type with lambda chain restriction.

I rise to say that as surgeons we should encourage our patients to have the Whipple procedure. That I am alive 2.5 years after operation and once again doing Whipples and hepatectomies myself, should prompt you to encourage patients to resume their presurgical lifestyle.

I wonder if the change in resectability rate and the noted decrease in mortality rate can be correlated with the advent of the CT scan, and with this time, did you note some decreasing time interval from symptoms or signs suggesting the malignancy to the time of diagnosis?

DR. RONALD K. TOMPKINS (Los Angeles, California): The worry I have with this report, which covers more than 40 years, is that some nondiscriminating reader may seize the overall mortality figures for that period of time rather than focusing on the current excellent results that have been reported, and use those data in a reference dated 1989 to promote some alternative therapeutic modality. That is something we have to continue to fight as we look at the comparative morbidity and mortality statistics that are quoted by endoscopists, radiologists, and other pseudosurgeons.

The authors indicated that no patient with distal bile duct cancer survived more than 5 years. This varies from our own experience and that of others, and I wonder if they could explain it.

They also reported eight common bile duct resections without Whipple procedures in this series of distal bile duct tumors. That is a rather unusual operation and I wonder if they would comment on whether they would continue to recommend that procedure.

They also state that the intent to cure at operation was a significant factor in survival. We have not favored palliative Whipple procedures in our institution, and we have also been disappointed in the results of total pancreatectomy, which we no longer recommend.

We agree with the authors that radical resection of the head of the pancreas should be reserved for those patients who clinically appear curable at the time of operation, and therefore, I would ask them how they now have improved their intraoperative staging methods to more accurately select those patients for curative resection. Finally because 76% or more of their patients underwent palliative procedures, I wonder if they would tell us briefly their techniques for management of these patients, whether they favor cholecystojejunostomy, or choledochojejunostomy, and whether they do gastric bypass on all of these patients.

DR. FABRIZIO MICHELASSI (Closing discussion): I will try to answer all the questions. Dr. Trede and several other discussants have underlined the fact that our series extends for 41 years. It is the price we paid to analyze a large number of patients, and therefore, to give significance to our statistical analysis, but when we went back and broke the 41 years into several periods, we noticed, indeed, that the only thing that changed overall was the perioperative mortality rate. The perioperative mortality rate, which was incredibly high in the first 10 or 20 years, as I mentioned in the presentation and in the manuscript, decreased to 5% during the last decade.

On the other hand, if you look at the group of patients in whom tumors were resected, the 5-year survival rate does not significantly change during the 41 years of the study. Furthermore of the four patients who survived more than 5 years after resection of an adenocarcinoma of the pancreas, two of them, therefore 50%, died after 5 years, reminding us that 5-year survival does not necessarily mean cure from adenocarcinoma of the pancreas.

We, too, analyzed all the resected tumors and specimens with the help of one senior pathologist, and in that effort one tumor that had been diagnosed as originating from the head of the pancreas became ampullary cancer.

When we analyzed the cohort of patients who also received chemotherapy and radiation therapy, we did not find any statistical significance in their outcome.

The resectability rate in the head of the pancreas, Dr. Frey, has clearly decreased during the last 40 years, and in the last decade I believe we have been more stringent in resecting these patients. I believe that the lesser intraoperative mortality rate at our institution is mainly due to the fact that this technically challenging operation is now performed more accurately by fewer surgeons with less operative blood loss and in shorter times; and for that, we agree totally with the findings presented by John Cameron 2 years ago at this Association. Moreover our ability to support the patients has increased greatly with the implementation of ICU care and parenteral alimentation.

We believe total pancreatectomy has the same mortality rate, if not higher, than a Whipple procedure. It does not give an advantageous survival rate over a Whipple procedure, and indeed, our data on the multicentricity of adenocarcinoma of the pancreas do not support the use of total pancreatectomy.

Finally to answer the comments of Dr. Tompkins, I think that the paper should be viewed not from the 20% overall mortality rate, but from the 5% mortality rate that has been achieved in the last 10 years, which is also in agreement with other series. I think that with a 5% rate of mortality, most of these tumors should be resected when resectable, with the understanding that although this will be a palliative procedure in 90% of patients, this is the best palliation we can obtain.

We do not clearly advocate local resection of common bile duct tumors, rather a Whipple procedure, and the intraoperative staging, I think, is in line with the criteria used by other centers.

Regarding the technical aspects of palliation, *i.e.*, cholecystojejunostomy or choledochojejunostomy, or whether to do a gastroenterostomy, the decision at surgery is based on the location of the tumor and on the predictability of possible future morbidity.

Chronic Compartment Syndrome

An Unusual Cause for Claudication

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Chronic Compartment Syndrome (CCS) is usually caused by overuse injury in well-conditioned athletes (particularly runners). Less common causes of CCS include blunt trauma, venous insufficiency, and tumor. CCS is clinically manifested as claudication, tightness, and occasional paresthesia. Unlike other forms of overuse injury (tendonitis, stress fracture), CCS does not respond to rest, anti- inflammatory medications, or physical therapy. The diagnosis of this condition is confirmed by elevated compartment pressures (normal < 15 mmHg; CCS > 20 mmHg). The only effective treatment is surgical compartment release. Two hundred nine patients have been surgically treated for CCS, 100 by subcutaneous fasciotomy (group I) and 109 by open fasciectomy (group II). These procedures were usually performed in ambulatory surgery using local anesthesia. Patients treated by open faciectomy instead of subcutaneous fasciotomy had fewer early postoperative wound complications (6% *vs.* 11%) and fewer late recurrences (2% *vs.* 11%).

INTERMITTENT CLAUDICATION IS commonly associated with elderly persons and is rarely diagnosed in young healthy adults with chronic leg pain. Atypical claudication can occur without clinical evidence of venous insufficiency or arterial occlusive disease because of a condition called Chronic Compartment Syndrome (CCS).[1-4] CCS is most commonly associated with overuse injury in well-conditioned athletes (particularly runners), but it can occur in patients with blunt limb trauma, or after acute and/or chronic venous insufficiency. Unlike other exertional injuries such as periostitis, stress fracture, or tendonitis, CCS does not respond to rest, anti-inflammatory medications, or physical therapy. The only effective therapy is surgical compartment release. Symptoms of CCS include severe muscle cramping, tightness, and occasional paresthesias that can seriously effect athletic levels of performance and in some circumstances can progress to acute neuromuscular injury. Knowledge of CCS is not widespread. However the problem is not uncommon and it is becoming more prévalent in this physical fitness-oriented generation. This report describes appropriate diagnostic tests for patients suspected of having CCS, explains indications for surgical intervention, and presents arguments for using fasciectomy instead of fasciotomy to treat CCS.

Materials and Methods.

Since 1976, 209 patients have been surgically treated for symptoms of CCS at the University of Wisconsin-Madison. The majority were athletes (187, or 89%) referred from our Sports Medicine Department, and the rest had a history of blunt limb trauma (14, of 7%), venous insufficiency (6, or 3%), or soft-tissue tumor (2, or 1%). These patients (96 male, 113 female) were young (mean age, 22 years) and had long-standing symptoms (mean, 24 months) that would abate or completely disappear after extended rest but reappear again with exercise. Medical treatment, including physical therapy, icing, and the use of anti-inflammatory medicines failed to significantly alter the severity of symptoms until physical activity was restricted. The most common symptoms included claudication (188 patients, or 90%), muscle group tightness (125 patients, or 60%), and parasthesias (52 patients, or 25%). The diagnosis of CCS was based on clinical history and confirmed in most cases by elevated compartment pressures. Although the Whiteside technique has been routinely used to measure compartment pressures, we prefer to use the hand-held Stryker Digital Computer System, which provides an accurate and less cumbersome method

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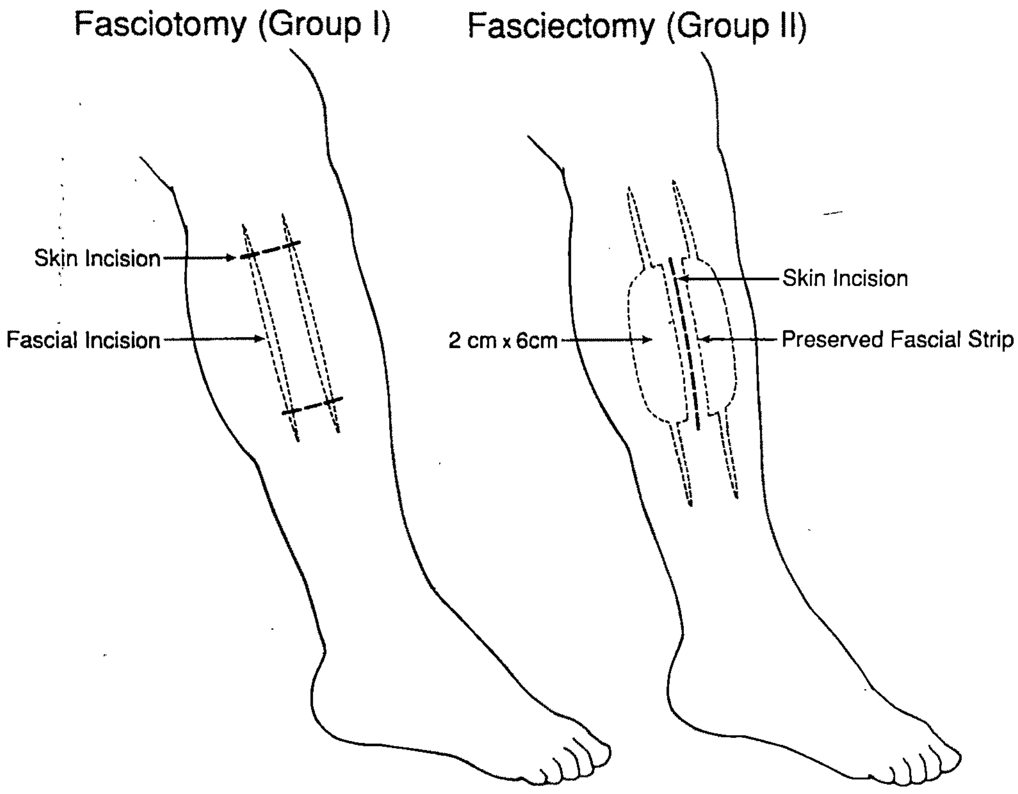

Fasciotomy (Group I)

Fasciectomy (Group II)

FIG. 1. Surgical compartment release techniques for the anterior and lateral compartments. Group I: Subcutaneous fasciotomy is performed using transverse skin incisions proximal and distal over the symptomatic compartment. Compartment fascia is incised by subcutaneously passing the scissors between the skin incisions. Group II: Open fasciectomy is performed using one linear incision over the medial one third of the anterior lateral surface of the leg. An elipse of fascia approximately 6 cm long and 2 cm wide is removed from the anterior and the lateral compartment, leaving a strip of fascia over the intermuscular septum. This strip protects the superficial peroneal nerve from injury or scar adherence. Extended compartment release can be achieved by proximal and distal subcutaneous fasciotomy performed under direct vision.

of obtaining compartment pressures.[4] Our experience is that normal resting compartment pressures in the lower leg are less than 15 mmHg, borderline pressures are between 16 and 20 mmHg, and pressures above 25 mmHg are markedly abnormal and uniformly consistent with CCS.[2,3,5] If patients have borderline pressures, repeat measurements should be performed after they have undergone treadmill stress or have run until symptoms develop. Patients with incipient CCS will show marked postexercise increases in compartment pressure and a prolonged return to the baseline (> 10 minutes). Accurate diagnosis of CCS requires that occult vascular disease be excluded as a cause of claudication symptoms. Noninvasive testing is routinely done to rule out vascular disorders that may occur in young adults, including premature atherosclerosis, popliteal entrapment, and chronic venous insufficiency. Resting and postexercise Pulse Volume Recordings (PVR), which provide plethysmography data and segmental limb pressure indices, are used to screen for intrinsic arterial occlusive disease. The PVR technique can also be used to screen for extrinsic compression of the popliteal artery (popliteal entrapment) by having the patient extend the knee and then dorsi flex and platar flex the foot. We performed arteriography when results of arterial screening tests were abnormal. We performed venous Doppler and Impedence Plethymography (IPG) tests on all patients who had limb swelling in conjunction with their complaints of claudication to rule out venous insufficiency.[6] Diabetic screening and EMGs were performed on patients with paresthesias to detect any peripheral nerve injury. Bone scans were performed selectively on patients who had bone pain along with muscle complaints to identify coexistent periostitis or stress fractures.[7] MRIs were done when patients were suspected of having post-traumatic intramuscular hematomas or CCS symptoms associated with a tumor mass.

We used surgical compartment release to treat patients with CCS when athletically induced symptoms persisted despite prolonged rest and aggressive medical management, or when the severity of claudication complaints worsened to the point that the patient's routine daily activities were adversely affected. The onset of paresthesias and the development of resting pressures greater than 25 mmHg were indications for prompt compartment release. Recreational athletes who developed CCS symptoms were encouraged to change sports or at least to modify the intensity and duration of their workouts as an alternative to surgery. In our experience most individuals involved in competitive athletics were unwilling or unable to accept behavior or training modification as a permanent means of controlling their clinical symptoms.

We performed surgical compartment release by subcutaneous fasciotomy in 100 patients (group I) and by open fasciectomy in 109 (group II) (Fig. 1). The superficial compartment releases in group I (anterolateral, posterior superficial) and the distal deep posterior releases were performed as out-patient procedures in ambulatory surgery using local anesthesia, while the proximal deep posterior releases were done as in-patient procedures. We performed 77 ambulatory surgical procedures; 23 were done the same day the patient entered the hospital. Subcutaneous fasciotomy was performed using transverse skin incisions placed strategically at the proximal and distal limits of the compartment to assure complete release. Linear skin incisions were only used to release the deep posterior compartments. Mean follow-up for this group is now 48 months.

Open fasciectomy was used to treat primary compartment syndromes as well as recurrences after subcutaneous fasciotomy in 109 patients (group II). Open fasciectomy was performed through linear incisions made parallel to the long axis of the compartment. In most cases we used local anesthesia. The linear skin incision provided better exposure and allowed for generous excision of fascia and precise control of muscle bleeding points, and made peripheral nerve injury much less likely. An ellipse of fascia 6 cm to 8 cm long and 2 cm to 3 cm wide was routinely excised and combined with extended subcutaneous fasciotomy under direct vision, assuring complete compartment release (Figs. 2A and B). Mean follow-up for this treatment group is now 36 months.

Results

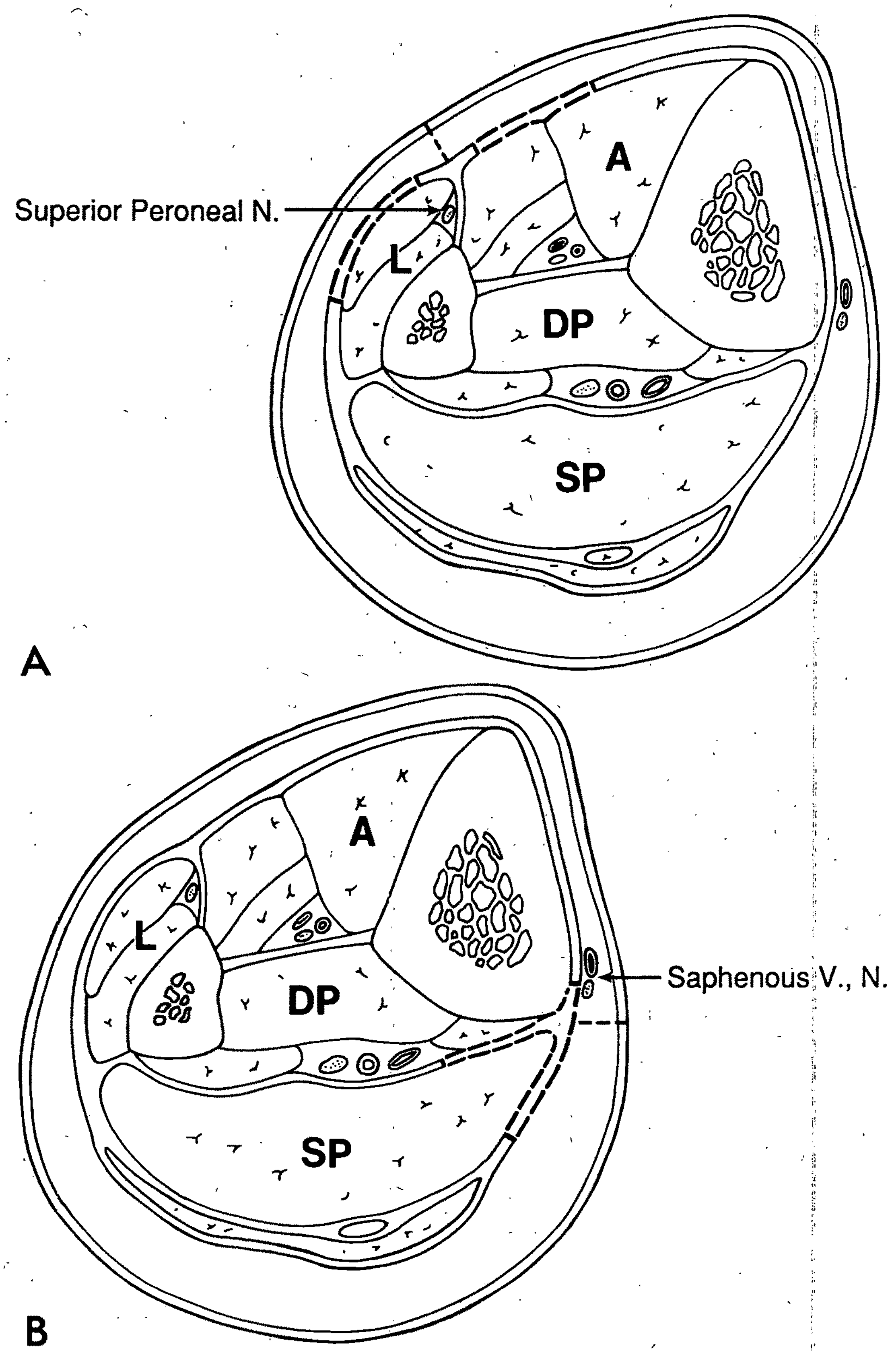
Most of the patients treated for CCS were athletes (187 patients, or 89%) who developed symptoms because of overuse injury. Other causes for CCS included blunt trauma, venous insufficiency, and soft-tissue tumor. In all we surgically released 511 symptomatic compartments. CCS was unilateral in 87 (41%) patients and bilateral in 122 (59%). The distribution of symptoms among the 511 affected myofascial compartments was as follows: anterolateral 245 (48%), deep posterior 204 (40%), and superficial posterior 62 (12%). Paresthesias occurred in 52 patients (25%) and were most commonly associated with the deep posterior compartment (39 patients) or anterolateral compartment (13 patients).

Although we routinely performed noninvasive vascular tests, only ten patients (5%) showed abnormal results. (Six abnormal IPGs suggested severe venous insufficiency, and four positional PVR changes suggested possible popliteal entrapment.) Angiograms performed on the patients with abnormal positional PVR tests showed no evidence of anatomic entrapment, but they did show external compression of the popliteal artery at the level of the soleus muscle in the deep compartment. Bone scans were performed on 20 patients who had bone pain (10%). Ten scans were positive for stress facture (four) or periostitis (six), and ten were negative. Patients with positive bone scans were not candidates for compartment release unless symptoms persisted after acute bone scan findings normalized. MRI scanning was useful for demonstrating intramuscular hematomas associated with blunt trauma (four patients) and for diagnosing soft-tissue tumors associated with CCS (two patients: one neurofibroma, one sarcoma).

In group I subcutaneous fasciotomy was performed on 100 patients with 233 symptomatic compartments. Eleven patients (11%) had 17 intraoperative or early postoperative complications. The most serious of these was a transection of the posterior tibial artery during a distal deep posterior compartment release. This vascular injury was successfully treated with an interposition vein graft. The most common problems were wound hematomas (5) and infections (4), but the most bothersome for patients were cutaneous sensory nerve injuries (3) (superficial peroneal nerve, saphenous nerve, and sural nerve). Other complications included thrombophlebitis (1), lymphocoele (3), and seroma (1). A total of 55 postoperative hospital days of care were required to treat these problems. Eleven patients (11%) developed recurrent symptoms in 16 compartments treated by fasciotomy. One third of these occurred within 3 months of surgery and were related in most cases to postoperative hematomas. The rest occurred within one year as a result of fascial scarring or herniation of muscle through the fasciotomy site. Most of the recurrences (13 of 16, or 80%) involved the anterolateral compartments and were successfully treated by an open fasciectomy. New symptoms developed in the distribution of previously unaffected compartments in five patients (5%).

In group II, open fasciectomy combined with selective extended subcutaneous fasciotomy was performed in 109 patients with 278 symptomatic compartments. Six patients (5.5%) developed eight postoperative wound complications (hematoma 5, cellulitis 2, seroma 1) that required a total of four in-hospital postoperative treatment days. There were no vascular or cutaneous sensory nerve injuries. Three patients developed delayed peripheral neuropathy (2 transient, 1 permanent) secondary to wound scar nerve entrapment. Two patients (2%) developed recurrent symptoms in the distribution of previously treated compartments (deep posterior). New CCS symptoms developed in untreated compartments in six patients (5.5%). These were successfully treated with open fasciectomy.

The best clinical results, regardless of the surgical release technique used (fasciotomy or fasciectomy), were obtained in patients who developed chronic compartment symptoms as a result of overuse injury. One hundred sixty-five of 177 patients in this category (93%) were completely cured. Four of the six patients with venous insufficiency (66%) were completely relieved of their compartment symptoms after open fasciectomy and the postoperative use of compression support with elastic stockings. Two



FIGS. 2A and B. These cross-sectional illustrations of the distal lower extremity muscle compartments (L = lateral compartment; A = anterior compartment, DP = deep posterior compartment, SP = superficial posterior compartment) demonstrate locations of fascial excisions required for release of the anterolateral and posterior compartments.

The superficial peroneal and long saphenous nerves are cutaneous branches that can be easily traumatized or encased in wound scar unless they are protected. Postoperative neuritis can negate any benefit derived from successful compartment release. Fascia overlying the intramuscular septum should be perserved so as to protect the superficial peroneal nerve from direct trauma or scar encasement. When a medial approach is used for posterior compartment releases, skin incisions should be placed posterior to the saphenous vein and nerve, and dissection around these structures should be avoided to reduce the probability of intraoperative trauma or postoperative scar entrapment.

other patients had minor relief. Only 8 of 14 patients who developed CCS as a complication of blunt trauma to the lower extremity (57%) and 1 of 2 patients with CCS symptoms related to expanding soft-tissue tumors in the lower extremity (50%) were cured by surgical compartment release and tumor excision.

Histologic examinations of the excised fascia specimens demonstrated increased thickness without inflammation

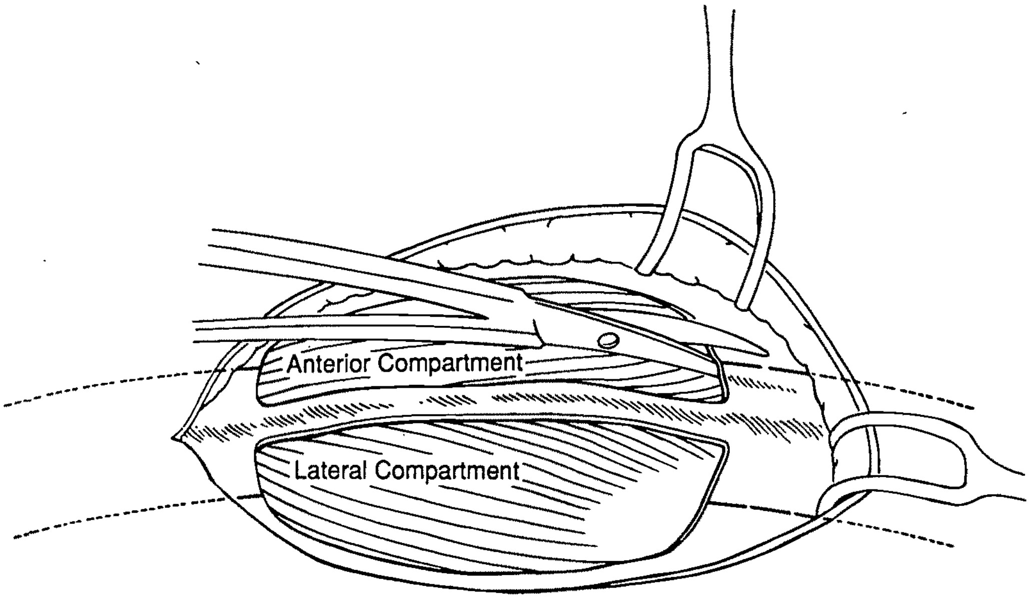


FIG. 3. Open faciectomy with extended subcutaneous fasciotomy is the procedure of choice to release the anterior and lateral compartments because it allows a more complete and precise decompression and reduces the likelihood of scar recurrence. Postoperative bleeding and neurovascular injuries have been significantly reduced because of the better exposure provided by a linear skin incision.

in 40% of cases, inflammatory changes with muscle scarring in 14%, and normal-appearing fascia without obvious abnormalities in 46%.

Despite technical differences in the extent of the surgery, there were no significant recovery differences between the two groups for uncomplicated cases. Patients returned to work or school and were ambulatory within 48 hours. Postoperative swelling was common and required elastic compression support for ten days to 2 weeks. Stretching exercises were started 1 week after surgery, and most patients were jogging 4 or 5 weeks after surgery. Return to full athletic capacity took 2 to 3 months.

Discussion

CCS is underdiagnosed and should be considered in young claudicants with normal vascular studies. CCS most commonly results from overuse injury in distance runners and athletes exposed to significant impact stress to lower extremities (basketball and football players, gymnasts and hurtlers). Occasionally, however, CCS may develop as a complication of blunt trauma, venous hypertension, or soft-tissue tumor expansion in lower extremities. Unlike the acute compartment syndrome, CCS rarely causes permanent neuromuscular injury, probably because discomfort restricts the patient's activity enough to prevent a prolonged increase in compartment pressure. Although abnormally elevated compartment pressures (>15 mmHg) occur in most patients (85%) with CCS, pressures much above 25 mmHg are uncommon in patients who are asymptomatic at rest. In symptomatic acute compartment syndromes, pressures usually exceed 40 mmHg. Compartment pressures in normal patients can increase to three or four times baseline values after vigorous activity, but they rapidly return to normal within a few minutes. Maximum postexercise pressures rarely exceed 50 mmHg. In patients with CCS, abnormally elevated baseline pressures may triple or quadruple after strenuous exercise, raising maximum compartment pressure to as high as 100 mmHg. Sustained pressures of this magnitude can cause circulatory damage to muscles and nerves. Rapid pressure decline with restricted activity probably explains why more patients do not progress to an acute form of the compartment syndrome.[2,5,7,8] It should be pointed out that diagnostic pressure measurements are safe and easy to perform when the anterolateral and posterior superficial compartments are being evaluated. However blind transcutaneous pressure measurements are not recommended for assessment of deep posterior compartments because of the potential for neurovascular injury.

It is reasonable to assume that the symptoms of claudication, parasthesia, and postexercise muscle group tightness associated with CCS are caused by local neuromuscular compression and ischemia. Increased muscle compartment pressure can be caused by several different factors, including muscle hypertrophy, altered fascia compliance associated with changes in fascial thickness and elasticity, myofacial scarring, venous hypertension, and post- traumatic soft-tissue inflammation. Unlike exertional injuries such as stress fracture, tendonitis, or periostitis, CCS can not be cured by nonsurgical methods of treatment. Although CCS symptoms improve temporarily with rest, anti-inflammatory medications, and physical therapy, symptoms quickly return once vigorous physical activity is resumed.[8-11] The only effective treatment for this condition is surgical compartment release. The objective of surgical therapy is to permanently reduce intracompartmental pressure. The technique most commonly used to treat CCS is subcutaneous fasciotomy. More recent clinical experience suggests that open fasciectomy is a safer and more effective treatment.[12] Open fasciectomy has fewer postoperative complications and fewer recurrences than blind subcutaneous fasciotomy. Open fasciectomy is done through a skin incision made parallel to the long axis of the muscle compartment. This incision improves exposure, makes identification of anatomic structures more precise, allows for direct control of bleeding points, and makes it much easier to perform a fasciectomy and extended subcutaneous fasciotomy under direct visualization. Better exposure reduces the hazards of intraoperative trauma to neurovascular structures. Fasciectomy combined with extended subcutaneous fasciotomy allows for complete decompression of the muscle compartment and greatly reduces the possibility of a recurrent compartment syndrome secondary to postoperative scarring (Fig. 3). Although fasciectomy is a more extensive procedure than fasciotomy, postoperative hospitalization, early complication rates, and late recurrences have been significantly reduced with little or no effect on the time required for rehabilitation.

We are now conducting prospective studies to determine whether there may be long-term functional differences between clinically successful fasciectomy and fasciotomy procedures. Our impression thus far is that no significant reductions in strength or endurance occur as a result of fasciectomy. Physiologic and histochemical evaluations of fascia from patients with CCS are being compared with specimens taken from comparable age groups requiring fasciectomies as part of orthopedic reconstructive surgery. We hope that these studies will allow us to better understand why some patients develop CCS and why others do not, and allow us to determine whether long-term functional differences between fasciotomy and fasciectomy exist.

Clinicians should be aware of CCS and consider it as a possible cause of claudication in young adults. This condition will not improve without surgery. Surgery is more effective for patients with CCS caused by overuse injury than for patients with CCS caused by trauma, venous hypertension, or tumor. Open fasciectomy causes fewer complications and fewer recurrences than closed subcutaneous fasciotomy and should be considered the surgical procedure of choice for treating CCS.

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DISCUSSION

DR. ROBERT W. BARNES (Little Rock, Arkansas): I am indebted to Dr. Turnipseed and his colleagues for providing me with one more reason not to jog. I am pleased that they have apprised us of this unique disorder that is somewhat analagous to mimo-causalgia or sympathetic dystrophy, which likewise can cause chronic, disabling, painful syndromes, which are often unrecognized by physicians and which can also be cured with appropriate therapy.

In reviewing the manuscript, I have three concerns about this study and three questions for the authors.

My first concern relates to the fact that we are not provided with detailed results of compartmental pressures at rest or after exercise in normal individuals and asymptomatic athletes or other subjects matched for age, sex, and causative factors similar to the patients reported. Second the method of determining the deep posterior compartmental pressure is not clear. My final concern relates to the implication that open fasciectomy is superior to semiclosed fasciotomy in the absence of evidence that these procedures were carried out concurrently or at random and in the absence of data reported in life table format.

My first question is to ask if the authors could correlate the development of symptomatic chronic compartment syndrome with inadequately supervised acute exposure to excessive muscular exercise. Second has the recent abuse of anabolic steroids contributed to an increased incidence of this syndrome? Finally, how can one adequately decompress the deep posterior compartment by fasciectomy under local anesthesia?

DR. F. WILLIAM BLAISDELL (Sacramento, California): I have a problem with this syndrome.

It is hard for me to imagine that muscle hypertrophy would be such as to crowd a compartment because the fascia should dilate or stretch in response to any chronic muscle enlargement.

I could accept the problem if it is the result of some type of fascial abnormality, that is, injury to the fascia that resulted in thickening so that the fascia could not enlarge as muscle hypertrophy develops.

I would ask whether there was any evidence on pathologic examination of the specimens that the fascia was abnormal. Also were any studies done of the fascia using ultrasound or CT that might have indicated if there was fascial abnormality?

DR. WILLIAM D. TURNIPSEED (Closing discussion): I would like to show a slide first addressing Dr. Blaisdell's concern about the true etiology of this condition.

We have tried to understand this problem in greater detail and have, in fact, looked and are looking at the fascia both in regards to its histochemical composition and to its morphology to better understand why some patients in the absence of any visual documentation of abnormality developed this condition.

We have been able to ascertain that almost one half of the patients have a mechanical explanation for this condition, such as inflamed, traumatized fascia with myofascial scarring or thickening, as shown here.

(Slide) This is normal fascia that measures about 0.06 mm. This specimen taken from one of our patients is about 0.25 mm. There seems to be a subgroup of these patients who have abnormalities in the fascia caused by repeated trauma with thickening and inflammation. However I think there are other causes for fascial abnormalities. We are now looking at some mechanical studies that may allow us to determine whether collagen content, elastin content, and other histochemical properties will, in fact, alter the compliance of fascia when the muscles look normal and the fascia looks normal, but the condition exists.

Dr. Barnes asked questions regarding the technique for deep compartment release. The deep compartment consists of a proximal and distal component. The distal deep compartment is second to the anteriolateral compartment as the most common site of symptoms. It is clinically manifest by paresthesias on the plantar surface of the foot, and sensation of tightness and aching deep behind the tibia.

Release of the distal deep compartment can be done under local anesthesia. It is important to stay away from the saphenous vein because the nerve can become entrapped in scar if you get too close to it. Sensory nerve entrapment can be almost as distressing as the compartment syndrome. The incision should be made posterior to the medial malleolus where the muscle hangs off the bone. The operation requires complete release of the superficial muscles from the tibia. You have to look at the back of the bone and see the flexor digitorum and the posterior tibialis muscle to be sure that the release is complete.

(Slide) This is the gastroc muscle. The soleus often inserts way down on the tibia just above the ankle. This is the flexor digitorum. You have to take all of these muscles down and look at the back of the tibia before you know you are in the right place. This is all done under local anesthesia. The patients go home the same day and it is very simple to do.

Dr. Barnes asked about the proximal deep compartment. This release is done under spinal or general anesthesia.

(Slide) This is the technique for proximal deep compartment release in patients who have symptomatic popliteal artery compression. It is like the thoracic outlet syndrome. What happens is that the fascial sling of the soleus and the flexor mechanism of the gastroc and the plantaris crush the artery and the nerve against the condyle of the tibia.

By taking the soleus down, removing that fascial band of the sling, and resecting the plantaris muscle, decompression of the area is achieved. We have treated intercollegiate athletes who were disabled and subsequently have been able to return to very successful seasons.

The use of steroids has not been a major problem in etiology of CCS. I think that steroids are useful for achieving muscle mass. Although runners sometimes use them, abuse is not common in recreational or most competitive runners.

Poor training techniques can result in acute injuries because of aggressive activity in a short period of time without proper preparation. These injuries include tendonitis, stress fracture, or acute compartment syndrome. Usually these individuals are put to rest with resolution of their symptoms within a short period of time. Chronic compartment syndrome is not related to acute injury, but more often is seen in well-conditioned athletes with overuse injuries.

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Annals of Surgery
Department of Surgery
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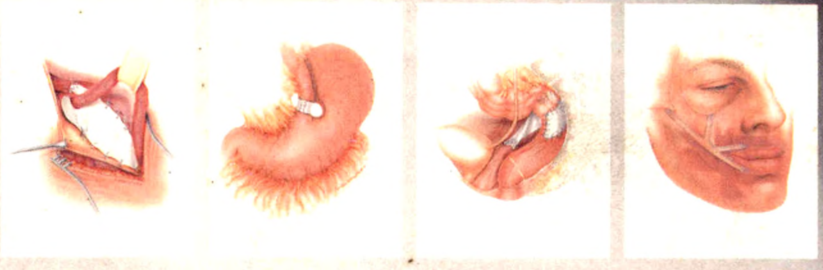

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TREATMENT: CEFOTAN® (cefotetan disodium) is indicated for the therapeutic treatment of the following infections when caused by susceptible strains of the designated organisms:
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Lower respiratory tract infections caused by *Streptococcus pneumoniae* (formerly *D pneumoniae*), *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Haemophilus influenzae* (including ampicillin-resistant strains), *Klebsiella* species (including *K pneumoniae*), and *E coli.*
Skin and skin structure infections caused by *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis, Streptococcus pyogenes* and *Streptococcus* species (excluding enterococci), and *E coli.*
Gynecologic infections caused by *Staphylococcus aureus** (including penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis, Streptococcus* species (excluding enterococci), *E coli, Proteus mirabilis, Neisseria gonorrhoeae, Bacteroides* species (excluding *B distasonis, B ovatus, B thetaiotaomicron*), *Fusobacterium* species,* and gram-positive anaerobic cocci (including *Peptococcus* and *Peptostreptococcus* species*).
Intra-abdominal infections caused by *E coli, Klebsiella* species (including *K pneumoniae**), *Streptococcus* species (excluding enterococci), and *Bacteroides* species (excluding *B distasonis, B ovatus, B thetaiotaomicron*).
Bone and joint infections caused by *Staphylococcus aureus.**
*Efficacy for this organism in this organ system was studied in fewer than ten infections.

Specimens for bacteriological examination should be obtained in order to isolate and identify causative organisms and to determine their susceptibilities to cefotetan. Therapy may be instituted before results of susceptibility studies are known; however, once these results become available, the antibiotic treatment should be adjusted accordingly.

In cases of confirmed or suspected gram-positive or gram-negative sepsis or in patients with other serious infections in which the causative organism has not been identified, it is possible to use CEFOTAN concomitantly with an aminoglycoside. Cefotetan combinations with aminoglycosides have been shown to be synergistic in vitro against many Enterobacteriaceae and also some other gram-negative bacteria. The dosage recommended in the labeling of both antibiotics may be given and depends on the severity of the infection and the patient's condition.

NOTE: If CEFOTAN and an aminoglycoside are used concomitantly, renal function should be carefully monitored, especially if higher dosages of the aminoglycoside are to be administered or if therapy is prolonged, because of the potential nephrotoxicity and ototoxicity of aminoglycosidic antibiotics. Although, to date, nephrotoxicity has not been noted when CEFOTAN was given alone, it is possible that nephrotoxicity may be potentiated if CEFOTAN is used concomitantly with an aminoglycoside.

PROPHYLAXIS: The preoperative administration of CEFOTAN may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures that are classified as clean contaminated or potentially contaminated (eg, cesarean section, abdominal or vaginal hysterectomy, transurethral surgery, biliary tract surgery, and gastrointestinal surgery).

The prophylactic dose of CEFOTAN should be administered 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, CEFOTAN should be administered intravenously after the clamping of the umbilical cord.

If there are signs and symptoms of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate therapeutic measures may be initiated.

CONTRAINDICATIONS
CEFOTAN is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS
Before therapy with CEFOTAN is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefotetan disodium, cephalosporins, penicillins, or other drugs. This product should be given cautiously to penicillin-sensitive patients. Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. If an allergic reaction to CEFOTAN occurs, discontinue the drug. Serious acute hypersensitivity reactions may require epinephrine and other emergency measures.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad-spectrum antibiotics may alter normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin in vitro.

Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated. When the colitis is not relieved by drug discontinuance, or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile.* Other causes should also be considered.

PRECAUTIONS
GENERAL: As with other broad-spectrum antibiotics, prolonged use of CEFOTAN may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection does occur during therapy, appropriate measures should be taken.

In common with many other broad-spectrum antibiotics, CEFOTAN may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment or poor nutritional state, the elderly and patients with cancer. Prothrombin times should be monitored in patients at risk and exogenous vitamin K administered as indicated.

CEFOTAN should be used with caution in individuals with a history of gastrointestinal disease, particularly colitis.

INFORMATION FOR PATIENTS: As with some other cephalosporins, a disulfiram-like reaction characterized by flushing, sweating, headache, and tachycardia may occur when alcohol (beer, wine, etc.) is ingested within 72 hours after CEFOTAN administration. Patients should be cautioned about the ingestion of alcoholic beverages following the administration of CEFOTAN.

DRUG INTERACTIONS: Although to date nephrotoxicity has not been noted when CEFOTAN was given alone, it is possible that nephrotoxicity may be potentiated if CEFOTAN is used concomitantly with an aminoglycoside.

DRUG/LABORATORY TEST INTERACTIONS: A false positive reaction for glucose in urine may occur with Benedict's or Fehling's solution.

As with other cephalosporins, high concentrations of cefotetan may interfere with measurement of serum and urine creatinine levels by Jaffe reaction and produce false increases in the levels of creatinine reported.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Although long-term studies in animals have not been performed to evaluate carcinogenic potential, no mutagenic potential of cefotetan was found in standard laboratory tests.

Cefotetan has adverse effects on the testes of prepubertal rats. Subcutaneous administration of 500 mg/kg/day (approximately 8-16 times the usual adult human dose) on days 6-35 of life (thought to be developmentally analogous to late childhood and prepuberty in humans) resulted in reduced testicular weight and seminiferous tubule degeneration in 10 of 10 animals. Affected cells included spermatogonia and spermatocytes; Sertoli and Leydig cells were unaffected. Incidence and severity of lesions were dose-dependent; at 120 mg/kg/day (approximately 2-4 times the usual human dose) only 1 of 10 treated animals was affected, and the degree of degeneration was mild.

CEFOTAN® (cefotetan disodium)

Similar lesions have been observed in experiments of comparable design with other methylthiotetrazole-containing antibiotics and impaired fertility has been reported, particularly at high dose levels. No testicular effects were observed in 7-week-old rats treated with up to 1000 mg/kg/day SC for 5 weeks, or in infant dogs (3 weeks old) that received up to 300 mg/kg/day IV for 5 weeks. The relevance of these findings to humans is unknown.

USAGE IN PREGNANCY: Pregnancy Category B: Reproduction studies have been performed in rats and monkeys at doses up to 20 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefotetan. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

USAGE IN NURSING MOTHERS: Cefotetan is excreted in human milk in very low concentrations. Caution should be exercised when cefotetan is administered to a nursing woman.

PEDIATRIC USE: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
In clinical studies, the following adverse effects were considered related to CEFOTAN therapy.
Gastrointestinal symptoms occurred in 1.5% of patients; the most frequent were diarrhea (1 in 80) and nausea (1 in 700).
Hematologic laboratory abnormalities occurred in 1.4% of patients and included eosinophilia (1 in 200), positive direct Coombs' test (1 in 250), and thrombocytosis (1 in 300).
Hepatic enzyme elevations occurred in 1.2% of patients and included a rise in SGPT (1 in 150), SGOT (1 in 300), alkaline phosphatase (1 in 700), and LDH (1 in 700).
Hypersensitivity reactions were reported in 1.2% of patients and included rash (1 in 150) and itching (1 in 700).
Local effects were reported in less than 1.0% of patients and included phlebitis at the site of injection (1 in 300), and discomfort (1 in 500). During postmarketing experience with CEFOTAN, anaphylactic reactions and transient thrombocytopenia have been reported.

DOSAGE AND ADMINISTRATION
TREATMENT: The usual adult dosage is 1 or 2 grams of CEFOTAN administered intravenously or intramuscularly every 12 hours for 5 to 10 days. Proper dosage and route of administration should be determined by the condition of the patient, severity of the infection, and susceptibility of the causative organism.

GENERAL GUIDELINES FOR DOSAGE OF CEFOTAN

Type of Infection	Daily Dose	Frequency and Route
Urinary Tract	1-4 grams	500 mg every 12 hours IV or IM 1 or 2 g every 24 hours IV or IM 1 or 2 g every 12 hours IV or IM
Other Sites	2-4 grams	1 or 2 g every 12 hours IV or IM
Severe	4 grams	2 g every 12 hours IV
Life-Threatening	6* grams	3 g every 12 hours IV

*Maximum daily dosage should not exceed 6 grams.

PROPHYLAXIS: To prevent postoperative infection in clean contaminated or potentially contaminated surgery in adults, the recommended dosage is 1 or 2 g of CEFOTAN administered once, intravenously, 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, the dose should be administered as soon as the umbilical cord is clamped.

IMPAIRED RENAL FUNCTION: When renal function is impaired, a reduced dosage schedule must be employed. The following dosage guidelines may be used.

DOSAGE GUIDELINES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

Creatinine Clearance mL/min	Dose	Frequency
>30	Usual Recommended Dosage*	Every 12 hours
10-30	Usual Recommended Dosage*	Every 24 hours
<10	Usual Recommended Dosage*	Every 48 hours

*Dose determined by the type and severity of infection, and susceptibility of the causative organism.

Alternatively, the dosing interval may remain constant at 12 hour intervals, but the dose reduced to one-half the usual recommended dose for patients with a creatinine clearance of 10-30 mL/min, and one-quarter the usual recommended dose for patients with a creatinine clearance of less than 10 mL/min.

When only serum creatinine levels are available, creatinine clearance may be calculated from the following formula. The serum creatinine level should represent a steady state of renal function.

$$\text{Males:} \quad \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/100 mL)}}$$

$$\text{Females:} \quad 0.9 \times \text{value for males}$$

Cefotetan is dialyzable and it is recommended that for patients undergoing intermittent hemodialysis, one-quarter of the usual recommended dose be given every 24 hours on days between dialysis and one-half the usual recommended dose on the day of dialysis.

HOW SUPPLIED
CEFOTAN is a dry, white to pale yellow powder supplied in vials containing cefotetan disodium equivalent to 1 g and 2 g cefotetan activity for intravenous and intramuscular administration. The 1 g dose is available in 10 mL and 100 mL vials, and the 2 g dose is available in 20 mL and 100 mL vials. CEFOTAN is also available in a pharmacy bulk package of 10 g in 100 mL vials. The vials should not be stored at temperatures above 22°C and should be protected from light.

1 g in 10 mL vial (NDC 0038-0376-10); 2 g in 20 mL vial (NDC 0038-0377-20); 1 g in 100 mL vial (NDC 0038-0376-11); 2 g in 100 mL vial (NDC 0038-0377-21); 10 g in 100 mL vial (NDC 0038-0375-10).

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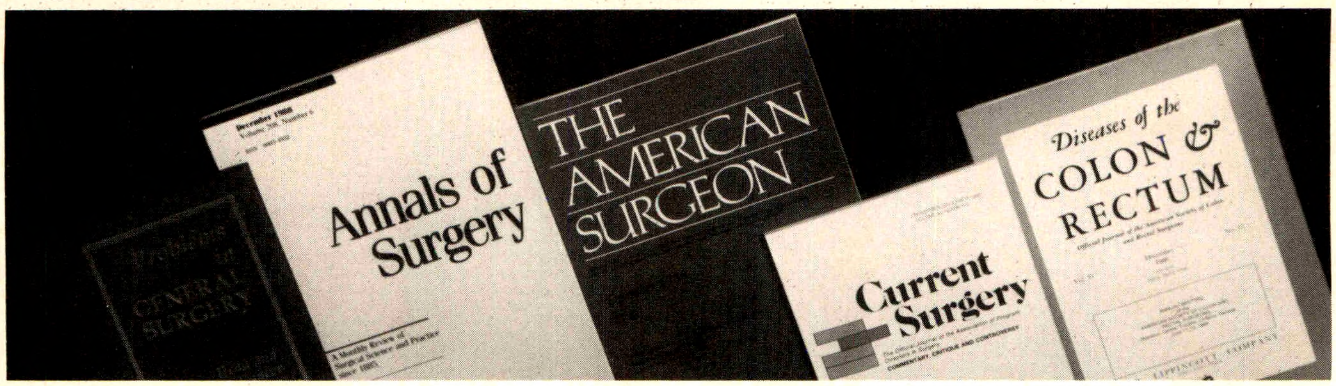

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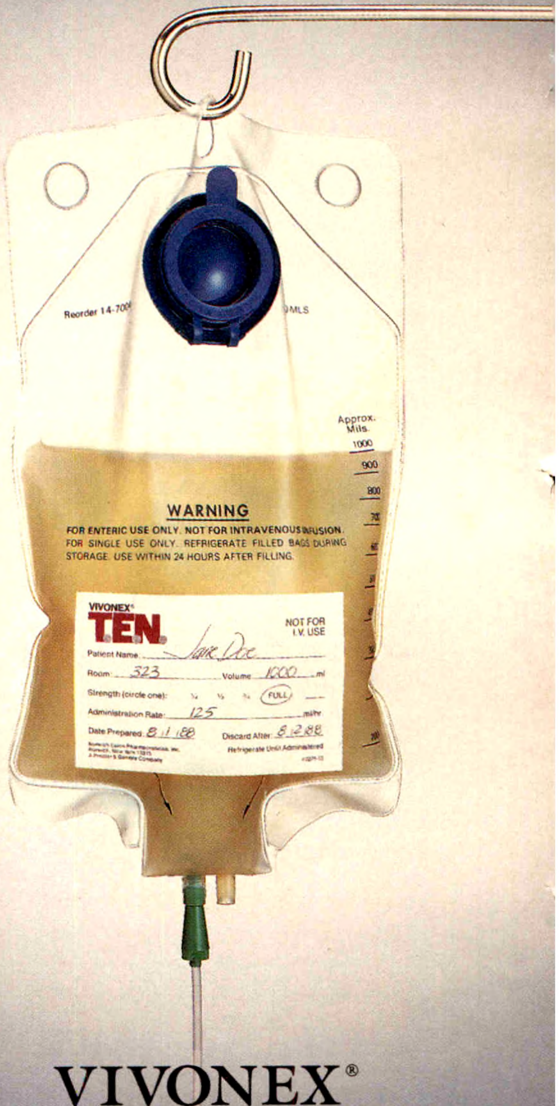
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What's New
In General Surgery

Extracorporeal Shockwave Lithotripsy of Gallstones

Possibilities and Limitations

HENK VERGUNST, M.D.,* ONNO T. TERPSTRA, M.D.,* KOEN BRAKEL, M.D.,† JOHAN S. LAMÉRIS, M.D.,†
MARK VAN BLANKENSTEIN, M.D.,‡ and FRITZ H. SCHRÖDER, M.D.§

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Recently extracorporeal shockwave lithotripsy (ESWL) has been introduced as a nonoperative treatment for gallstone disease. Except for lung damage, no significant adverse effects of ESWL of gallbladder stones have been observed in animals. In clinical use ESWL of gallbladder stones is now confined to 15% to 30% of symptomatic patients. To achieve complete stone clearance, ESWL of gallbladder stones must be supplemented by an adjuvant therapy. ESWL of bile duct stones is highly effective and can be considered in patients in whom primary endoscopic or surgical stone removal fails. Second generation lithotriptors allow anesthesia-free (outpatient) treatments, but the clinical experience with most of these ESWL devices is still limited. The likelihood of gallbladder stone recurrence is a major disadvantage of ESWL treatment, which raises the issue of cost-effectiveness. ESWL for cholelithiasis is a promising treatment modality with good short-term and unknown long-term results.

EXTRACORPOREAL SHOCKWAVE LITHOTRIPSY (ESWL) has revolutionized therapy of urolithiasis. Despite concern about the long-term effectiveness and possible inducement of hypertension,[1] this noninvasive treatment has gained worldwide acceptance. After the convincing success of ESWL in urology, it was tempting to extend this technology to the treatment of gallstones.

Gallstone disease represents an important health care problem in the western world. The estimated prevalence of gallstones is about 10% to 15% and increases with advancing age.[2] Although many gallstones do not cause symptoms and need not be treated,[3-5] gallstone disease is a major cause of hospitalization for surgical treatment. In the United States annually more than $1 billion is spent on treatment of gallstones, mainly for the 500,000 cholecystectomies performed each year.[6] Since Langenbuch performed the first cholecystectomy in Berlin in 1882,[7] operative removal of the gallbladder has become the standard therapy for patients with symptomatic gallbladder stones. Cholecystectomy has an overall mortality rate of 0.6% to 1.3%, increasing from 0.2% in patients younger than 70 years to 5% in patients older than 70 years.[8-11] A safe and effective treatment for many patients, the morbidity rate of cholecystectomy is 10% to 33%,[11,12] it is uncomfortable for the patient, it requires hospitalization, and usually causes invalidity for 1 month.[13] To reduce the morbidity and mortality rates, as well as the cost, several nonoperative therapeutic alternatives have become

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available for both cholecystolithiasis and choledocholithiasis. Although still in its infancy, ESWL of gallstones is one of the most promising noninvasive treatment modalities for cholelithiasis. In this review article we will discuss the possibilities and the limitations of ESWL for the management of gallstone disease.

Principle of Shockwave Application

The basic physical principles have been described in detail elsewhere,[14,15] and presently only the essential clinical facts have been compiled. Shockwaves cause high pressure amplitudes to increase within nanoseconds and to respond to the known physical laws of acoustics. If water is used as a transmission medium, focused shockwaves spread through the body evenly without severely damaging the tissues because the acoustical impedance of most body tissues is close to that of water. At its focus point, the wave impact against the stone liberates short-term high-energy mechanical stresses because of the abrupt change in acoustical impedance. This causes tear-and-shear forces, which, together with the formation of cavitation bubbles in the surrounding medium on the surface of the stone, eventually lead to the disintegration of the stone.[16,17]

The original waterbath lithotriptor developed by Dornier generates shockwaves by an underwater electric spark discharge in the one focus of an elliptical reflecting cavity that are condensed in the second focus. Positioning of the stone in this second focus occurs with a fluoroscopic guidance system. Today a second generation of ESWL devices is on the market, with the same concept of underwater generation of shockwaves (Table 1). They apply varying combinations of techniques for shockwave generation, focusing, and target imaging apparatus. Most manufacturers have replaced the water immersion tank with a compressible water bag that enables contact skin positioning of the shockwave applicator. Nearly all are more compact in design, operate at lower costs, require simpler patient positioning, and many have the potential capability for treating gallbladder stones.[18]

Experimental Application of ESWL

Abdominal shockwave exposition in rats, as well as exposure of eventrated isolated organs (liver, kidney, intestine), did not cause pathologic changes.[15,19,20] Shockwaves directed to kidneys or to implanted stones in the renal pelvis of pigs and dogs produced only slight and predominantly transient traumatization of the exposed kidneys. These dose-dependent alterations (small hematomas and/or diffuse intraparenchymal hemorrhages) are restricted to the high-pressure field of the shockwaves and do not affect renal function.[15,20–24] In acute experiments on dogs, shockwaves on the liver and gallbladder also caused slight changes: small ecchymoses on the liver surface and gallbladder wall. Petechial hemorrhages may also occur on the serosal surface of the pancreas and duodenum. These minor gross and histologic changes were not considered a contraindication to applying shockwaves for gallstone destruction in humans.[25–28] On the other hand, if shockwaves strike on a tissue–air interface, in the lung, for example, damage may occur due to release of energy caused by the large difference in acoustical impedance of air and

TABLE 1. *Second Generation Extracorporeal Lithotriptors (Adapted from Ferrucci[18] and updated to October 1988)*

Manufacturer	Model	Shockwave Generation	Focusing	Target Imaging	Coupling	Suitability
Wolf (W. Germany)	Piezolith 2300	PE	spherical array	US	mini-tank	GB
Technomed International (France)	Sonolith 3000	SGE	ellipsoid	US	mini-tank	GB
EDAP (France)	LT 01	PE	spherical array	US	waterbag	GB
Siemens (W. Germany)	Lithostar	EM	acoustic lens	x-ray	waterbag	CBD
	Lithostar Plus	EM	acoustic lens	x-ray + US	waterbag	GB + CBD
Medstone International (USA)	1050 ST	SGE	ellipsoid	x-ray ± US	waterbag	CBD (+GB)
Nitech (Denmark)		SGE	ellipsoid	US	waterbag	GB
Dornier Medizin Technik (W. Germany)	HM 4	SGE	ellipsoid	x-ray	waterbag	CBD
	MPL 9000	SGE	ellipsoid	US	waterbag	GB
	MFL 5000*	SGE	ellipsoid	x-ray	waterbag	CBD
Direx (Israel)	Tripter X1	SGE	ellipsoid	x-ray + US	waterbag	GB + CBD
Northgate (USA)	SD 3	SGE	ellipsoid	US	waterbag	GB
Diasonics (USA)	Therasonic	FE	spherical array	x-ray + US	waterbag	GB + CBD
Storz Medical (W. Germany)	Modulith SL 10	FE	sperical array	US	waterbag	GB
	Modulith SL 20	FE	spherical array	x-ray + US	waterbag	GB + CBD

* Also marketed as Philips MFL 5000 (The Netherlands)

PE, piezoelectric; SGE, spark-gap electrode; EM, electromagnetic; US, ultrasound; GB, gallbladder stones; CBD, common bile duct stones.

tissue. When the rat thorax was exposed to shockwaves, fatal lung damage was found.[15,19,20] ESWL of surgically implanted gallbladder stones in dogs also resulted in pulmonary damage (alveolar hemorrhage) involving areas just above the diaphragm in one third of the animals;[29] no animal died, and no hemoptysis was noted after shockwave application (Delius, written personal communication, 1988). These serious side effects are dependent on the shockwave pressure field. They do not occur when the lungs are more than 4 cm removed from the shockwave axis.[30] Other investigators have observed no changes or lesions in the right lung only in dogs autopsied one day after ESWL; no changes were observed in animals killed 14 days after treatment.[26,31] The differences in outcome of shockwave application can be explained by differences in shockwave pressure distribution in the acoustic fields generated by the various lithotriptors.

Differences in the physical characteristics of shockwave pulses generated by differing lithotriptors are also responsible for the variation in results of *in vitro* fragmentation studies of human gallstones.[32] Soft cholesterol stones with a low density, as assessed by computed tomography, required more discharges to fragment the stone than those with a high pigment and calcium content.[33,34] On the other hand, other studies revealed successful fragmentation regardless of the chemical composition or the calcium content of the stone and suggest that ESWL may be applied to all types of gallstones. The effectiveness of this therapy will then only be limited by the total stone burden and the time required to complete stone fragmentation. This corresponds well with the observation that the number of shockwaves required to bring about fragmentation of human gallstones *in vitro* correlated closely with the number, volume, weight, and diameter of the stones.[31,35–38]

Clinical Application of ESWL for Gallstones

Gallbladder Stones

The first successful ESWL treatment of patients with gallstones was reported by Sauerbruch and coworkers in 1986.[39] They treated nine patients with functioning gallbladders containing 1 to 3 symptomatic radiolucent stones that were not larger than 25 mm in diameter. All stones were disintegrated into sludge or fragments. At present more than 1000 patients with gallbladder stones, most of them in Germany, have undergone ESWL on different systems (Table 2).The selection of patients is usually determined according to the inclusion and exclusion criteria of the Munich group (Table 3).

Because only cholesterol stone fragments are susceptible to adjuvant dissolution therapy, patients with radiopaque, calcified stones have been excluded, with a few exceptions.[46–48]

Recently the results of the first 175 patients treated in Munich were published.[40] In this the best-documented series so far, 72% of patients with solitary stones 21 to 30 mm in diameter and 63% of those with two or three stones could be expected to be free of stones 1 year after lithotripsy and adjuvant oral dissolution therapy. Smaller stones disintegrated into smaller fragments than did larger stones. The success rate for single stones 20 mm or smaller in diameter was clearly higher than for larger and multiple stones. The disappointing results with multiple stones may be due to difficulties in sonographic identification of residual stones during ESWL treatment after disintegration of the first stone. The subsequent disintegration of the remaining stones may be less complete, resulting in larger residual fragments, the dissolution of which take a longer period. Although stones with a radiopaque rim could also be successfully disintegrated, more time was required for these stone fragments to disappear.

Complications have been few. Except asymptomatic petechiae at the entrance of shockwaves into the skin and incidental transient gross hematuria due to passage of shockwaves through the right kidney, no other adverse effects related to the administration of shockwaves were observed. Routine laboratory blood tests showed no significant changes, except a mild leucocytosis immediately after ESWL that normalized within 24 hours. Probably as a result of the passage of fragments, mild or moderate pancreatitis developed in two patients. Furthermore about one third of the patients suffered once or more frequently from mild biliary colicy pain, which was easily treated with spasmolytic agents. With the exception of diarrhea occurring in 4% of the patients, the adjuvant administration of oral bile acids did not cause adverse effects.

Biliary Duct Stones

The original clinical work done by Sauerbruch et al.[39] also suggested that common bile duct stones may be fragmented by ESWL without causing serious side effects. Subsequently their experience has been further extended and similar positive results of ESWL of common duct, intrahepatic, and retained cystic duct stones with both first and second generation lithotripsy devices have been accumulated in a number of patient series. ESWL of biliary duct stones in 346 patients resulted in an overall complete stone clearance rate of 63% to 100% (Table 4).

Most patients with bile duct stones that resist removal after endoscopic sphincterotomy can be treated by ESWL without general anesthesia; and ESWL may resolve life-threatening conditions, especially for high-risk and critically ill patients.[53,57,58] Significant adverse effects and alterations in laboratory tests, including liver and pancreas enzymes, usually do not occur. Transient hematuria is a

TABLE 2. *Results of ESWL of Gallbladder Stones*

First Author and References	No. of Patients	Type of Lithotriptor	Fragmentation (% of pts)	Adjuvant Treatment	Side Effects (% of pts)						Mean Follow-up	Stone free (% of patients)
					Cutaneous Petechiae	Biliary Colic	Transient Gross Hematuria	Pancreatitis	Cystic Duct Occlusion	Others		
Sackmann[40] Heberer[41] (Munich)	175–250	Dornier-HM 3 (modified) Dornier-MPL 9000	99	Urso + cheno*	14	35	3	2 (n = 5)	5	Incidental	6 months	80 post-ESWL
Greiner[42] (Wuppertal)	157	Dornier-HM 3 (modified)	94	Urso + cheno		25	5	3 (n = 5)	2 (n = 3)	Incidental	8.5 weeks	70–80 expected to be stone free at 12 months post-ESWL
Ponchon‡ (Lyon)	91	Technomed Sonolith 2000/3000	71	Urso + cheno		11	2	1 (n = 1)	2 (n = 2)	22 (only in first 20 pts treated with old type of SW-generator)[43] and 7%	6 months	50 post-ESWL
Pizzi[44] (Milano)	29	Siemens Lithostar	86	Urso				3 (n = 1)			—	—
Hood[45] (London)	38	Wolf Piezolith 2200/2300	89	Urso + cheno	11			3 (n = 1)		11	—	—
Manfredi‡ (Rome)	44	Technomed Sonolith 3000	80	Urso			No severe complications				4 months	—
Bory‡ (Lyon)	20	Tripter Direx-X1	75	Urso + cheno		No complications					—	—
Darzi[46] (Dublin)	37	EDAP-LT 01	—	Bile acids (?)		3 (n = 1)					—	14 (32 > 50 clearance) ? post-ESWL

Burhenne‡ (Vancouver)	48	Siemens Lithostar	90 (during first session)	No adjuvant therapy		2 (n = 1)		—	—
Peine[47] (Rochester)	8	Dornier-HM 3	50	MTBE†	No significant complications			—	75, 8–26 hrs post-ESWL
Mosnier[48] (Suresnes)	57	EDAP-LT 01	98	Urso + cheno	19		54	—	20, 1 month post-ESWL
Zuin[49] (Milano)	35	EDAP-LT 01	37 (fragm. ≤ 5 mm) (max 3 sessions)						
	35	Wolf Pfiezolith 2200/2300	43 (fragm. ≤ 5 mm) (max 3 sessions)						
Total	849		37–99						

* Urso, ursodeoxycholic acid; cheno, chenodeoxycholic acid
† MTBE, methyl-tert-butyl-ether.
‡ Personal communication, biliary lithotripsy; First International Symposium, July 11–13, 1988, Boston, MA.

common finding after ESWL of bile duct stones but is of little clinical significance.

Limitations of Biliary ESWL

Initially lithotripsy of gallstones was performed under general anesthesia, limiting ESWL to patients with a preoperative physical status compatible with class I or II of the American Society of Anesthesiologists.[39,59] Now intravenous analgosedation is sufficient for most patients, general or epidural anesthesia seldom being required. Treatments with piezoelectric lithotripsy devices are reported to be completely painless.[26,27,45] Nevertheless, depending on the type of lithotriptor, for certain patients intravenous opiate analgesia cannot replace adequate anesthetic techniques and the cooperation of an anesthesiologist (Schelling et al., unpublished data). Besides, unless triggered by the R-wave of ECG, the spark-gap systems especially can induce arrhythmias. Careful monitoring of the ECG is required, especially in patients with pre-existing cardiac rhythm disorders.

Anesthesia-free (outpatient) treatments have been made possible by lowering the total shockwave energy and by distributing the energy more diffusely at the skin surface. However the price for these technical adjustments is a lower initial stone fragmentation rate. For that reason more shockwaves are required, causing a longer duration of the treatment session or resulting in a high retreatment rate because patient tolerance is limited.

In contrast to kidney stones most gallstones are radiolucent. Fluoroscopic targeting of a nonopaque gallbladder stone is not possible unless the stone has been visualized by contrast opacification of the gallbladder by oral or intravenous cholecystography. Therefore targeting of gallbladder stones can be best accomplished by ultrasound, but this can be difficult or impossible in obese patients.

Gallbladder Stones

Several distinctions immediately arise between lithotripsy of gallbladder stones and urinary tract calculi.[18] After ESWL at least 90% of fragments of renal calculi pass spontaneously through the ureter. Complete spontaneous discharge of residual fragments after ESWL of gallbladder stones cannot be expected because sufficient disintegration can rarely be obtained. This is crucial because experimental and clinical investigations indicate that only fragments smaller than 2 mm to 3 mm in diameter can pass into the intestine without causing local trauma.[60,61] Besides, both the spiral valves in the cystic duct and the choledochoduodenal sphincter are anatomical barriers presenting potential sites of relative obstruction. Furthermore the common bile duct has no peristalsis and there is a pre-existing relative dysmotility of the gallbladder that is not altered by ESWL treatment.[62,63] These factors imply

TABLE 3. *Inclusion and Exclusion Criteria for ESWL of Gallbladder Stones*[40]

Inclusion Criteria	Exclusion Criteria
History of biliary pain	Acute cholecystitis, cholangitis, or pancreatitis
Solitary radiolucent gallbladder stone ≤30 mm, or up to three stones with similar total volume	Biliary obstruction or known bile duct stone Gastroduodenal ulcers
Gallbladder visualization by oral cholecystography	Coagulopathy or anticoagulants or aspirin
Stone positioning possible in the shockwave focus	Aneurysms or cysts in shockwave path
Shockwave avoids lung and bone	Pregnancy

that in addition to biliary colic, cholecystitis, cholangitis, and pancreatitis are possible serious complications.

Adjuvant therapy. The need for adjuvant treatment after ESWL of gallbladder stones has not been absolutely proved and is being investigated in the United States in a randomized clinical multicenter trial. For now it is likely that successful therapy of gallbladder stones will require a combination of ESWL and a subsequent adjuvant therapy to achieve complete stone clearance. This can be performed in three ways: (1) the use of oral dissolution therapy with bile acids (only cholesterol stones),[64] (2) percutaneous contact dissolution by direct transcatheter infusion into the gallbladder of solvents, the most promising of which is methyl-tert-butyl-ether (MTBE) (only cholesterol stones),[65,66] and (3) percutaneous drainage for evacuating the gallbladder (cholesterol and pigment stones).[67,68] Thus far bile acids have been used mainly as adjuvant management because they seem to offer the most simple and harmless treatment for remaining fragments of cholesterol stones. This implies that the nature of the stone must be known.

Dissolution by oral (or local) agents is greatly enhanced by preceding stone fragmentation.[41,69–71] Despite this enhancement the expensive oral dissolution therapy still must be continued for at least 6 to 12 months after primary therapy by ESWL. Therefore, notwithstanding the more invasive character, adjuvant percutaneous dissolution therapy might afford a favorable alternative.[47,72–74] For patients with large or numerous stones currently being excluded for ESWL treatment, contact dissolution with MTBE may broaden the applicability of ESWL. Moreover MTBE also seems to be useful after ESWL of partially calcified cholesterol stones.[47]

With pigment stones a combination of ESWL and a percutaneous evacuation technique, with which stone fragments are removed mechanically or by aspiration, is possible.[67,68] Further development of solvents for contact dissolution of pigment stones may also be a future possibility.[75–77]

Tissue damage. On anatomical grounds the pulmonary damage found in dogs should present less of a problem in humans and such damage has not yet been observed in patients.[29,31,40] Nevertheless ESWL has the potential for causing significant soft-tissue damage in the high-pressure area of the shockwaves around the focus.[25,27,78] Patients subjected to ESWL immediately before elective cholecystectomy have shown gross evidence of acute tissue injury at laparotomy. Oedema of the gallbladder wall together with vascular dilatation, several petechial hemorrhages, and variable mucosal denudation were found (Johnson et al., unpublished data).[27,78] With the exception of the mucosal denudation, these changes were absent from gallbladders excised 24 to 48 hours and 5 days after ESWL, which indicates that these changes may be rapidly reversible.[45] The presence of intact epithelium in the mouths of the mucosal crypts, as visualized by scanning electron microscopy, may serve as a source of viable cells for re-epithelialization. Multiple small hematomas, which can be detected in the parts of the liver parenchyma which are transversed by the shockwaves, disappear within a few days to 4 weeks.[25] These changes, which are comparable to the small perirenal and intraparenchymal hematomas observed after ESWL of kidney stones, are of no clinical importance.[25,79–82] However this implies that patients with coagulation disorders should be excluded from ESWL treatment. Relying on the data presented in Table 2, the incidence of pancreatitis, which can be considered an adverse effect of the administration of shockwaves as well as a complication due to passage of fragments, is small. This finding is rather surprising because the risk of acute pancreatitis is said to be increased in patients with microlithiasis of the gallbladder.[83] Thus far emergency cholecystectomy for acute cholecystitis has not been reported. Finally gas-filled intestines may cause ESWL-induced erosions in the upper gastrointestinal tract.[84]

Indications. Application of ESWL is limited to only 15% to 30% of patients with symptomatic gallbladder stones who are referred for therapy.[40,85] However the previously accepted selection criteria for ESWL of gallbladder stones (Table 3) seem to underestimate the number of suitable patients. Patients with stones larger than 30 mm in diameter, with more than three in number, and partially calcified stones have also been treated successfully,[40,46,47,51] but in light of the lower success rate other treatments may be more attractive. As to the mere histopathologic status, 60% of cholecystectomized patients who have no or very limited histologic changes in the gallbladder are potential candidates for ESWL.[86] In view of the diminishing need for anesthesia, it seems justified to extend this treatment to poor-surgical-risk patients, as recently reported.[53,57,58] Increasing experience and further improvement of lithotriptors may make ESWL of gallbladder stones possible for a larger population of patients. For now, however, it

TABLE 4. *Results of ESWL of Biliary Duct Stones*

First Author and References	No. of Patients	Location of Stones	Type of Lithotriptor	Complete Stone Fragmentation (% of pts)	Complete Stone Clearance (% of pts)	Side Effects	% of Patients
Heberer[41] (Munich)	51	common bile duct	Dornier-HM 3	—	80	not documented	
Sauerbruch[50] (multicenter trial)	113	(common) bile duct	Dornier-HM 3	1 treatm: 86 ≥ 2 treatm: 91	86	mild severe mortality*	29 8 0.9
Greiner[51] (Wuppertal)	36	(common) bile duct	Dornier-HM 3	—	97	sepsis (n = 1)	3
Staritz[34,52] (Mainz)	30	intrahepatic (5) common bile duct (25)	Siemens Lithostar	intrahepatic: 100 common bile duct: 70	—	cutaneous petechiae	—
Burhenne[53] (Vancouver)	8	common bile duct (4) cystic duct (remnant) (4)	Dornier-HM 3	75	75	short term fever (n = 3) mild hematuria (n = 2) transient hemobilia (n = 1)	38 25 13
Burhenne†	30	(common) bile duct	Siemens Lithostar	—	±75	not documented	
Terpstra[54] (Rotterdam)	13	common bile duct	Dornier-HM 3	100	100	transient hematuria small subcapsular hematoma of right kidney (n = 2)	77 15
Terpstra†	8	common bile duct	Siemens Lithostar	63	63	sepsis (n = 1) cutaneous petechiae (n = 1)	8 13
Faustini[55] (Milano)	14	(common) bile duct	Siemens Lithostar	100	100	none	
Ginestal-Cruz† (Lisbon)	16	(common) bile duct	Siemens Lithostar	69	69	cutaneous petechiae	69
Bory† (Lyon)	11	common bile duct	Direx Tripter-X1	91	91	not documented	
Fried[56] (Halifax)	16	(common) bile duct	Dornier-HM 3	94	88	transient hemobilia (n = 2) short-term elevation of AST and LDH transient hematuria (n = 1) cutaneous petechiae	12 most patients 6 81
Total	346			63–100			

* Mortality = 30 day mortality.

† Personal communication, biliary lithotripsy; First International Symposium, July 11–13, 1988, Boston.

is unlikely that gallbladder lithotripsy will equal ESWL in urology, which is now the standard treatment for urolithiasis for almost all patients.

Stone characteristics. For lithotripsy of gallbladder stones it is not sufficient to know whether gallstones are present or absent. At least the number and size of the gallstones must be known and cystic duct patency must be assessed. Plain abdominal x-rays are of limited value in predicting gallstone type[87] because there is a 14% chance that radiolucent stones are pigment stones.[88] As the fragments of pigment stones cannot be dissolved with the agents in use so far, it is important to predict gallstone composition more precisely. Computed tomography seems to be of great value in discriminating between radiolucent cholesterol and pigment stones, and thus in the prediction of susceptibility to adjuvant dissolution therapy.[89–91] The exact role of this and other tests in differentiating between cholesterol and pigment stones has not yet been established.[92,93] Before ESWL of patients with gallbladder stones is performed, an extension of the diagnostic work-up is needed. Sonography should be combined with the almost-obsolete-but-now-reviving method of oral cholecystography to establish the functional status of the gallbladder.

Recurrence. A significant drawback of each alternative for cholecystectomy and also of ESWL of gallbladder stones lies in the likelihood of stone recurrence. Although recurrence after ESWL has not been definitely assessed due to the relatively short follow-up period, experience with oral bile acid dissolution therapy suggests a 50% recurrence 5 to 7.5 years after complete disappearance of stone fragments.[94,95] This corresponds with the observed recurrence rate of 10% within 6 months after discontinuation of adjuvant dissolution therapy after preceding ESWL treatment.[41] The feasibility, effectiveness, and potential toxicity of long-term continuous low-dose or intermittent therapeutic-dose treatment with bile acids to prevent stone recurrence have not been conclusively investigated.[95,96] Oral administration of inhibitors of HMG-CoA-reductase, however, may be an interesting treatment to decrease the cholesterol excretion in the bile, thus reducing the chance of recurrence of gallstone disease. To prevent recurrent stone formation, the results of attempts of nonsurgical defunctionalization of the gallbladder by percutaneous occlusion of the cystic duct and ablation of the gallbladder by sclerosing agents are currently being evaluated in experimental models.[97–103] The results are promising and the first application in humans has recently been started (Becker, written personal communication, 1988).

Bile Duct Stones

Despite the potential of ESWL, the indications for ESWL treatment of bile duct stones will remain limited because there are other effective nonoperative treatment modalities such as endoscopic removal.[104,105] Therefore shockwave fragmentation should be considered only in patients in whom, after endoscopic sphincterotomy, stone extraction fails. This represents only 9% of all patients with bile duct stones referred for endoscopic removal.[50]

Unlike gallbladder stones, common bile duct stones are preferably localized by fluoroscopy rather than sonography.[106] To focus the shockwaves on the stone, bile duct stones have to be visualized, which is normally achieved by contrast injection through an endoscopically placed nasobiliary catheter.[41,50] This can also be performed by percutaneous transhepatic cholangiography.[53,54,56,107]

A treatment failure rate of 20% at the first session must be accepted (Sauerbruch, written personal communication, 1988). Failure of lithotripsy could not be predicted by analysis of the calculi before ESWL by computed tomography and did not depend on stone diameter. Interposition of bowel gas, which is likely to absorb shockwave energy, is possibly responsible for failure of treatment.[52] In approximately 75% of patients additional interventional procedures, like endoscopic extraction of remaining fragments, are needed to achieve complete fragment clearance.[50]

Problems and Perspectives

A number of problems still must be solved. A major question is how to measure efficacy of ESWL treatment of gallstones. Most reports mention fragmentation rates and/or stone clearance rates, but much obscurity still exists about the effects on symptoms. Thus far only symptomatic gallbladder stones have been treated. For comparison of the long-term results it would be desirable to use a clear definition of "symptomatic gallstones," as was recently established by a working party at the Gastroenterology Meeting in Rome.[108] While for a silent (asymptomatic) stone in the gallbladder an expectant approach may be best, some form of active treatment has been recommended for asymptomatic choledocholithiasis.[108]

In the event of recurrence, retreatment with ESWL or dissolution therapy must be considered, although it is still uncertain if all recurrent stones will again cause symptoms. This raises the question whether ESWL as primary therapy for gallbladder stones is cost-effective, at least for young patients. Significant cost savings have been realized by hospital discharge 24 hours after cholecystectomy.[109,110] For most of the healthy and relatively young patients, cholecystectomy, which provides a permanent cure at a small risk, remains the most cost-effective option. For patients older than 70 years, ESWL will probably be of greater importance because of the higher morbidity and mortality rates of surgical management. The possibility of ESWL treatment on an outpatient basis should also be taken into account. Analysis of the cost-effectiveness of lithotripsy of gallbladder stones *versus* conventional cholecystectomy requires further observations of long-term results. This goal can be best achieved in prospective randomized studies, which are being conducted in Sheffield, United Kingdom (Williams, written personal communication, 1988) and at our institution.

Although increasing steadily, experience with extracorporeal shockwave treatment of gallstones outside Germany is still limited, and the reports of results with second generation lithotriptors are based on small patient series. Most of these preliminary studies have only a short follow-up and are not well documented. The (adapted) Dornier renal lithotriptor has proved to be a device to treat gallstones in the gallbladder and in the common bile duct successfully without serious short-term adverse effects in selected patients. Thorough data on the potential risk of harmful side effects and efficacy of most second generation lithotripsy devices, however, are still lacking. Caution in the clinical application of new ESWL systems for treatment of cholelithiasis is mandatory. Basic experimental work on the pressure distribution in the focal area as well as to safety and efficacy must be done for each new lithotripsy apparatus before human biliary application is justified.[13]

In conclusion ESWL for gallstone disease is a promising noninvasive treatment modality with acceptable short-time risks and efficacy. Long-term results and possible late complications still must be assessed.

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Choledochoscopic Electrohydraulic Lithotripsy and Lithotomy for Stones in the Common Bile Duct, Intrahepatic Ducts, and Gallbladder

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Choledochoscopic lithotomy with the aid of electrohydraulic lithotripsy was performed in 40 patients, including 16 patients with choledocholithiasis, 15 with hepatolithiasis, and 9 with cholecystolithiasis. As a route for the choledochoscopy, a T-tube tract, external cholecystostomy, or jejunal limb of hepaticojejunostomy was used in nine patients, while percutaneous transhepatic biliary drainage followed by dilatation of the track was established in 31 patients. The largest cholesterol stone measured 55 mm by 33 mm and the largest bilirubinate stone measured 52 mm by 37 mm. The stones were disintegrated in all but one patient in whom choledochoscopic access to a gallstone was difficult due to deformity of the gallbladder. Complete removal of the stones was achieved in 38 of 39 patients. In a patient with hepatolithiasis, small stones located deep in inaccessible branches of the intrahepatic duct remained unremovable. There were no serious complications. Minor complications occurred, including bleeding from the bile duct mucosa in four patients and postprocedure chills and fever in three. Choledochoscopic lithotomy with electrohydraulic lithotripsy is efficient and useful to remove biliary calculi in patients who are poor surgical risks.

A VARIETY OF NONSURGICAL approaches for the treatment of cholelithiasis are available. Endoscopic sphincterotomy (EST)[1,2] and choledochoscopic lithotomy[3,4] have gained wide acceptance. However huge stones and impacted stones continue to present a technical problem. Chemical dissolution[5,6] and fragmentation of gallstones using extracorporeal shock wave[7] are receiving enthusiastic trials but are not always successful.

Previously we reported the use of electrohydraulic lithotripsy (EHL) under direct visual control during choledochoscopy to remove intrahepatic stones.[8] This report addresses the results of application of the EHL technique in a new series of 40 patients. The present series includes patients with calculi in the common bile duct, gallbladder, and the intrahepatic ducts.

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Materials and Methods

Patients

From June 1985 to June 1988, choledochoscopic electrohydraulic lithotripsy and lithotomy were performed in 40 patients with stones in the common bile duct, intrahepatic ducts, or gallbladder (Table 1). The series included 16 men and 24 women, ranging in age from 45 to 87 years. Eleven patients were between 70 and 80 years of age and seven patients were older than 80 years. All these patients had one or more reasons that rendered nonsurgical removal of the stones preferable (Table 1).

The size of the stone (stones) measured on direct cholangiograms was greater than 30 mm in diameter in 9 patients, between 20 mm and 30 mm in 10 patients, and between 7 mm to 20 mm in the remaining 21 patients. The stone was impacted at the distal common bile duct in 12 patients. Twenty-three patients had less than 4 stones, 6 patients had 5 to 10 stones, and 11 patients had numerous stones. Eleven patients had cholesterol stones, the largest of which measured 55 mm by 30 mm, while the other 29 patients had pigment stones, the largest of which measured 52 mm by 37 mm. Computed tomography performed in one half of these patients revealed distinct calcification of the stones in seven patients.

Common bile duct stones. Eight of 16 patients with common bile duct stones were high surgical risks; 4 patients were older than 80 years, 3 had a history of multiple

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TABLE 1. *Indications of Choledochoscopic Electrohydraulic Lithotripsy*

Indications	Remarks	Number of Patients
Choledocholithiasis	Residual stones with a biliary tube in place	5
	Extraction failed after EST*	5
	Difficult duodenoscopic approach	6
Hepatolithiasis	Polysurgery	4
	Biliary cirrhosis	4
	Retained stones	3
	Advanced age (over 77 years)	2
	Previous operation for gallbladder cancer	1
	Detected by chance without symptoms	1
Cholecystolithiasis	Advanced age	4
	Polysurgery	2
	Chronic renal failure	1
	Congestive heart failure	1
	Schizophrenia	1
Total		40

* EST, endoscopic sphincterotomy.

abdominal operations, 1 had spinal cord injury, and 1 had ischemic heart disease. Twelve of these patients had undergone cholecystectomy previously, while 4 patients had gallbladders with (1 patient) or without (3 patients) gallstones.

Five of the 16 patients had a T-tube (4 patients) or a percutaneous transhepatic biliary drainage (PTBD) tube (1 patient) in place. Five patients had had EST performed but duodenoscopic extraction had failed because the stones were huge (larger than 30 mm) in 3 patients, impacted and immobile in 1, or located beyond a bile duct stenosis due to chronic pancreatitis in 1 patient. The duodenoscopic approach was considered inadequate for various reasons in the other six patients. Two of these had the anomalous union of the pancreatic and bile ducts. One had undergone Billroth II gastrectomy. The stone was impacted at the distal common bile duct in one. The papilla was situated within a diverticulum in one. A huge stone (55 by 30 mm) occupied the entire lumen of the bile duct in another patient.

Intrahepatic stones. Fifteen patients had stones in the intrahepatic ducts. All but one patients with intrahepatic stones had a history of one or more biliary operations. Fourteen of the 15 patients had a reason for the nonoperative approach for removal of the intrahepatic stones (Table 1). An asymptomatic patient in whom the intrahepatic stones were detected by echography refused surgical treatment.

Fourteen of these 15 patients were considered to have primary hepatolithiasis, which was associated with common bile duct stones in four patients. Another patient had hepatolithiasis secondary to stenosis of the common hepatic duct injured at cholecystectomy 15 years before. In two patients, the intrahepatic stones were first discovered by T-tube cholangiography. Four patients had undergone EST for removal of common bile duct stones and one patient had transduodenal sphincteroplasty, but the intrahepatic stones were retained.

Gallbladder stones. Nine patients had stones in the gallbladder. Two of them presented with jaundice and cholangitis due to a so-called confluence stone and had PTBD performed (Fig. 1). Two other patients had an external cholecystostomy for acute cholecystitis; one of them had undergone transhepatic drainage of a liver abscess secondary to cholecystitis. The remaining five patients had percutaneous transhepatic gallbladder drainage (PTGBD) to provide a route for lithotomy. All of these nine patients were poor operative risks (Table 1).

Instruments

An electric surge current generator (Lithotron EL-21, Walz Elektronik Gmbh, Rohrdorf, West Germany) with a 4.5 French size lithotripsy probe was used. The intensity of discharge was usually set at 2 with a frequency of 20 per second. When the stone was hard, the intensity was increased to 3.

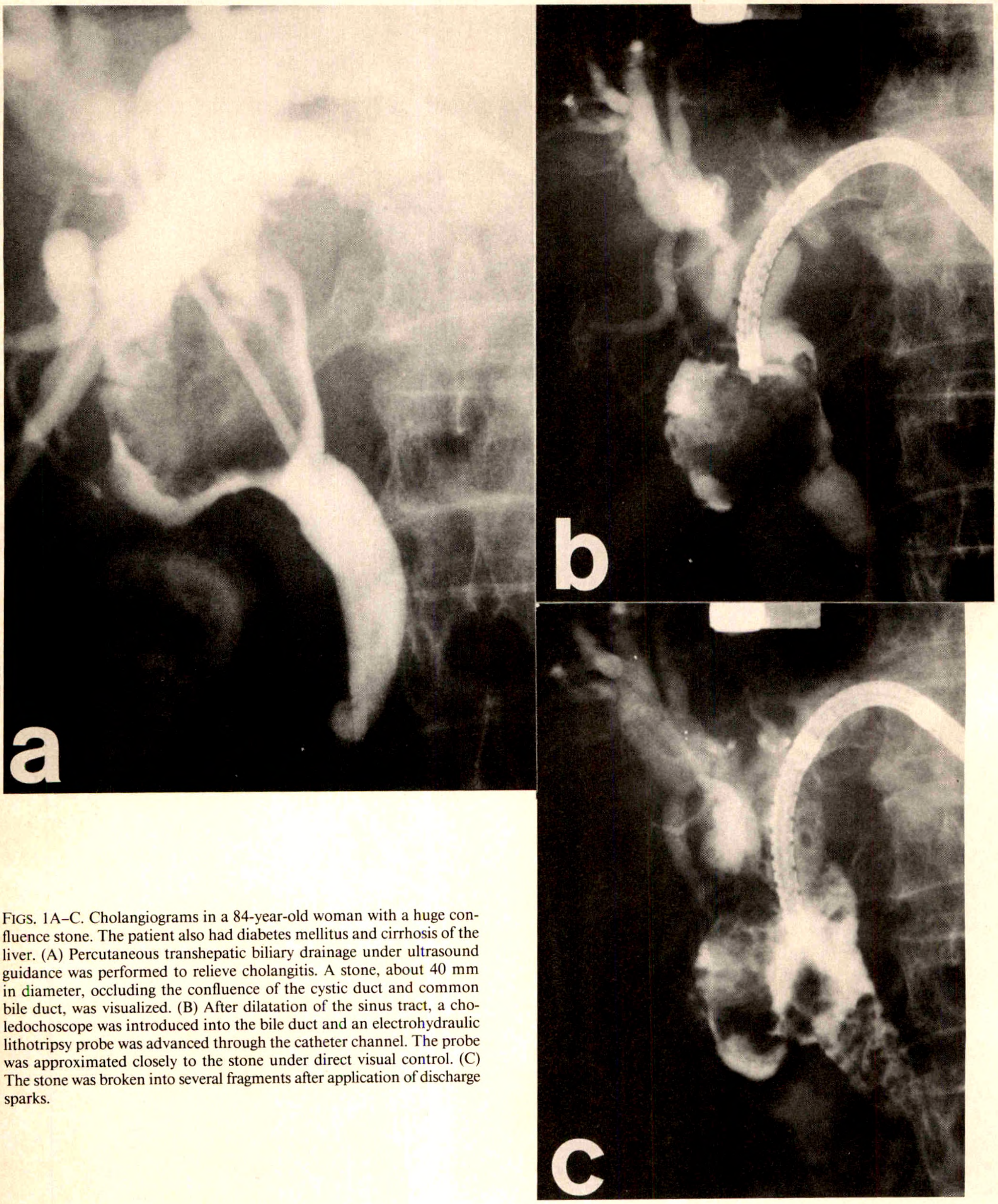
A small-caliber choledochofiberscope (4.8 mm, model CHF P10, Olympus Optical Co., Tokyo, Japan) was usually used. In cases in which the stones were larger than 25 mm in diameter, a choledochoscope with a larger diameter (6.5 mm, model CHF B3, Olympus Optical Co., Tokyo, Japan) was used, because more rapid infusion of saline through its larger biopsy channel permitted us to keep the endoscopic view clear during the procedure.

Routes for Choledochoscopy

Table 2 shows the routes for insertion of the choledochoscope and lithotripsy instruments. A PTBD tract was used after dilatation in 26 patients, a T-tube tract in 6, a PTGBD tract in 5, and an external cholecystostomy tract in 2 patients. In another patient, a blind end of the jejunal limb subcutaneously implanted at previous Roux-en-Y hepaticojejunostomy was reopened and used as a route for choledochoscopy.

Techniques

To establish the percutaneous transhepatic route, the intrahepatic duct or gallbladder was entered under ultrasonic guidance. Using a guide wire technique, a 7.2 French biliary drainage catheter for PTBD or a 10 French Malecot catheter for PTGBD (Cook, Inc., Markham, Ontario, Canada) was placed in the common bile duct or gallbladder, respectively. The catheter tract was dilated twice a



FIGS. 1A–C. Cholangiograms in a 84-year-old woman with a huge confluence stone. The patient also had diabetes mellitus and cirrhosis of the liver. (A) Percutaneous transhepatic biliary drainage under ultrasound guidance was performed to relieve cholangitis. A stone, about 40 mm in diameter, occluding the confluence of the cystic duct and common bile duct, was visualized. (B) After dilatation of the sinus tract, a choledochoscope was introduced into the bile duct and an electrohydraulic lithotripsy probe was advanced through the catheter channel. The probe was approximated closely to the stone under direct visual control. (C) The stone was broken into several fragments after application of discharge sparks.

week by replacing the catheter with a larger one by 2 French size. A 16 to 20 French (5.3 to 6.7 mm) sinus tract was obtained within 2 weeks.

Choledochoscopy was first attempted 3 weeks after operative or percutaneous biliary catheterization. The drainage catheter was removed, leaving a guide wire in

TABLE 2. *Routes for Choledochoscopic Electrohydraulic Lithotripsy*

Indications	Routes	Number of Patients
Intrahepatic stones	PTBD tract*	13
	T-tube tract	3
Common duct stones	PTBD tract	11
	T-tube tract	3
	Jejunal limb of hepaticojejunostomy	1
Gallbladder stones	PTGBD tract†	5
	External cholecystostomy	2
	PTBD tract	2

* PTBD, percutaneous transhepatic biliary drainage.
† PTGBD, percutaneous transhepatic gallbladder drainage.

the biliary tract. The choledochoscope was then introduced into the biliary tract over the guide wire placed in the catheter channel. When the sinus tract proved immature, further attempts for lithotomy were postponed for 1 week. Once maturation of the track was confirmed, the biliary tract was entered under direct visual control without the aid of the guide wire. After a gallstone was visualized, the lithotripsy probe was passed through the catheter channel, the tip was kept in the close proximity of the stone, and the discharge sparks were applied to the stone under direct vision. After the stone was disintegrated, a large fragment of the stone was grasped in a basket catheter and pulled out along with the choledochoscope through the sinus tract. This procedure was repeated to remove as many large fragments as possible. Small fragments were removed by irrigation and suction through the choledochoscope. The lithotripsy was performed once or twice a week, each session being limited to one hour.

Results

In all but one of the 40 patients the stones were disintegrated into sludge or fragments measuring 5 mm or less in diameter, yielding the overall success rate of 97% (Table 3). We were unable to fragment a stone impacted in the cystic duct in only one patient because it was unreachable by choledochoscopy. Fragmented stones were completely removed in 38 patients using the combined technique of basket extraction, irrigation, and suction. In only one patient with hepatolithiasis, stones remained in the small branches of the right posterior segmental duct because this area was difficult to approach through the PTBD tract established from the left lateral segmental duct (Fig. 2).

Most cases required multiple sessions of chledochoscopic lithotripsy and lithotomy. The number of sessions per patient was 4.5 ± 2.5 (mean ± SD), ranging from two to ten. The length from the first biliary catheterization until completion of lithotomy was 40 ± 12 days. These figures differed among three groups of patients, the smallest figures were in patients with common bile duct stones and largest were in patients with intrahepatic stones (Table 4).

In three of nine patients with gallbladder stones the fragments moved from the gallbladder to the common bile duct. The fragments further passed spontaneously into the duodenum in one patient within 1 week, but the fragments remained in the common bile duct for 2 weeks in two other patients, necessitating EST for removal of the fragments (Fig. 3). In one of the remaining six patients, the fragments stayed in the cystic duct. Because tortuosity of the cystic duct prohibited basket extraction of these fragments, irrigation with 500 mL of saline through the PTGBD catheter was used for five days after EST, resulting in clearance of the fragments.

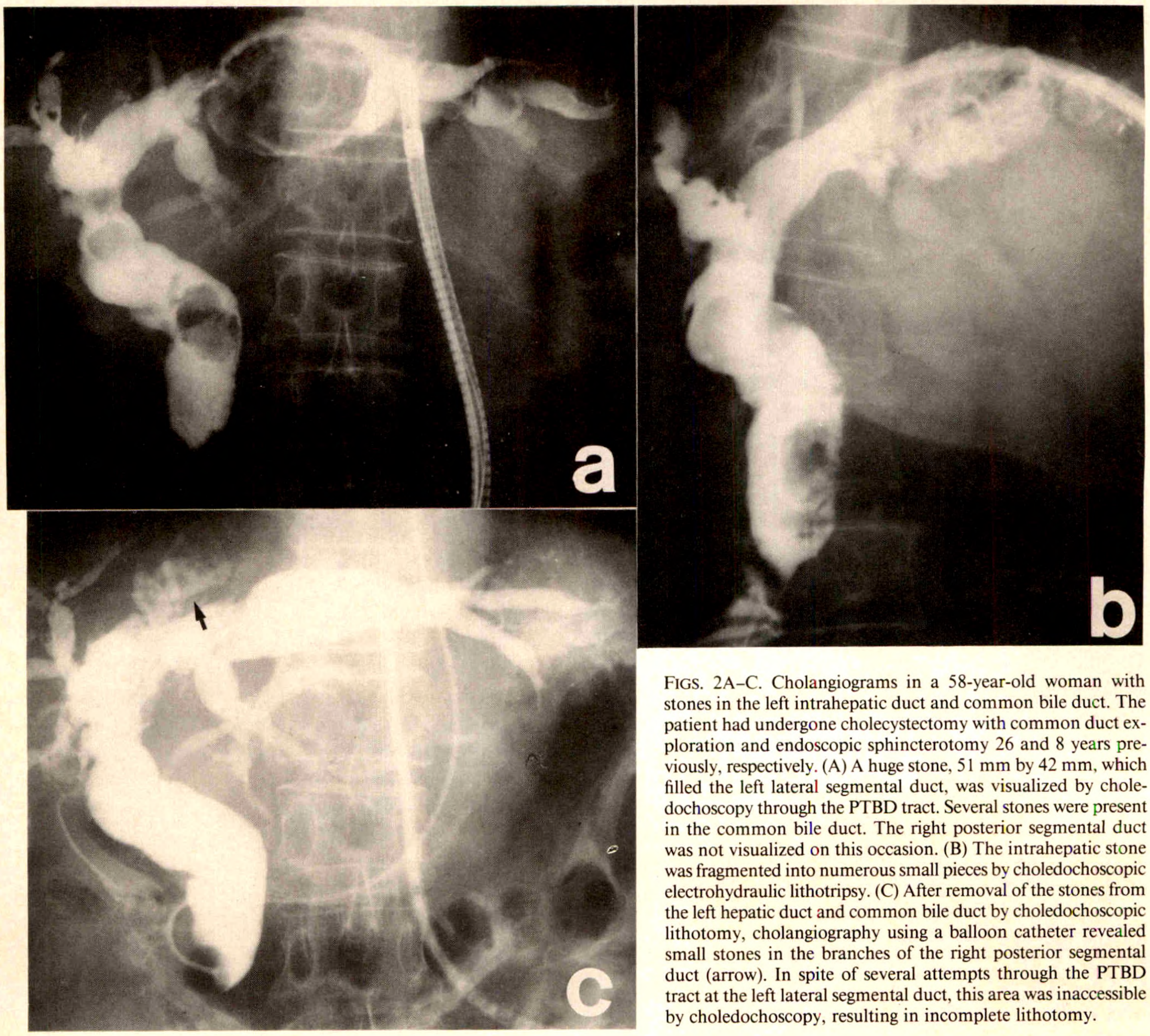
A firm sinus track formed within 3 weeks in 38 patients. Maturation of the track took 2 months in one of the other two patients because of hepatic congestion secondary to chronic heart failure, and 1.5 months in the other patient, in whom a silicon catheter of the Malecot type was used for maintenance of the sinus track because deep cannulation into the intrahepatic duct was prevented by the stones occupying the whole lumen.

The procedure was well tolerated by all the patients and caused no serious adverse effects. Minor bleeding from the mucosa of the bile duct occurred in four patients. In three of them, bleeding caused by scratching of the bile duct wall with the tip of the lithotripsy probe stopped spontaneously. Bleeding in another patient occurred when a stone packed in the left hepatic duct was fragmented by the right intercostal approach. The bleeding was controlled by compression with an 18 French catheter advanced into that duct over the guidewire under fluoroscopic control. Three patients had transient chills and fever after the procedure; this was probably due to cholangiovenous reflux caused by increased biliary pressure during saline infusion into the bile duct.

During the application of spark discharge the endoscopic view was often blurred by dispersion of small fragments and bubbles, particularly when the small-caliber choledochoscope (CHF P10) was used because the catheter channel was filled with the 4.5 French probe, which prevented irrigation with saline. This kind of difficulty was minimal when the larger choledochoscope (CHF B3) was used because of the larger catheter channel; however, the

TABLE 3. *Results of Choledochoscopic Electrohydraulic Lithotripsy*

Results/Complications	Number of Patients
Successful fragmentation	39 (97%)
Complete removal	38 (95%)
Incomplete removal	1
Intrabiliary bleeding	4
Chills and fever	3



FIGS. 2A–C. Cholangiograms in a 58-year-old woman with stones in the left intrahepatic duct and common bile duct. The patient had undergone cholecystectomy with common duct exploration and endoscopic sphincterotomy 26 and 8 years previously, respectively. (A) A huge stone, 51 mm by 42 mm, which filled the left lateral segmental duct, was visualized by choledochoscopy through the PTBD tract. Several stones were present in the common bile duct. The right posterior segmental duct was not visualized on this occasion. (B) The intrahepatic stone was fragmented into numerous small pieces by choledochoscopic electrohydraulic lithotripsy. (C) After removal of the stones from the left hepatic duct and common bile duct by choledochoscopic lithotomy, cholangiography using a balloon catheter revealed small stones in the branches of the right posterior segmental duct (arrow). In spite of several attempts through the PTBD tract at the left lateral segmental duct, this area was inaccessible by choledochoscopy, resulting in incomplete lithotomy.

sinus track had to be dilated up to 18 French, requiring several more days before choledochoscopy was attempted.

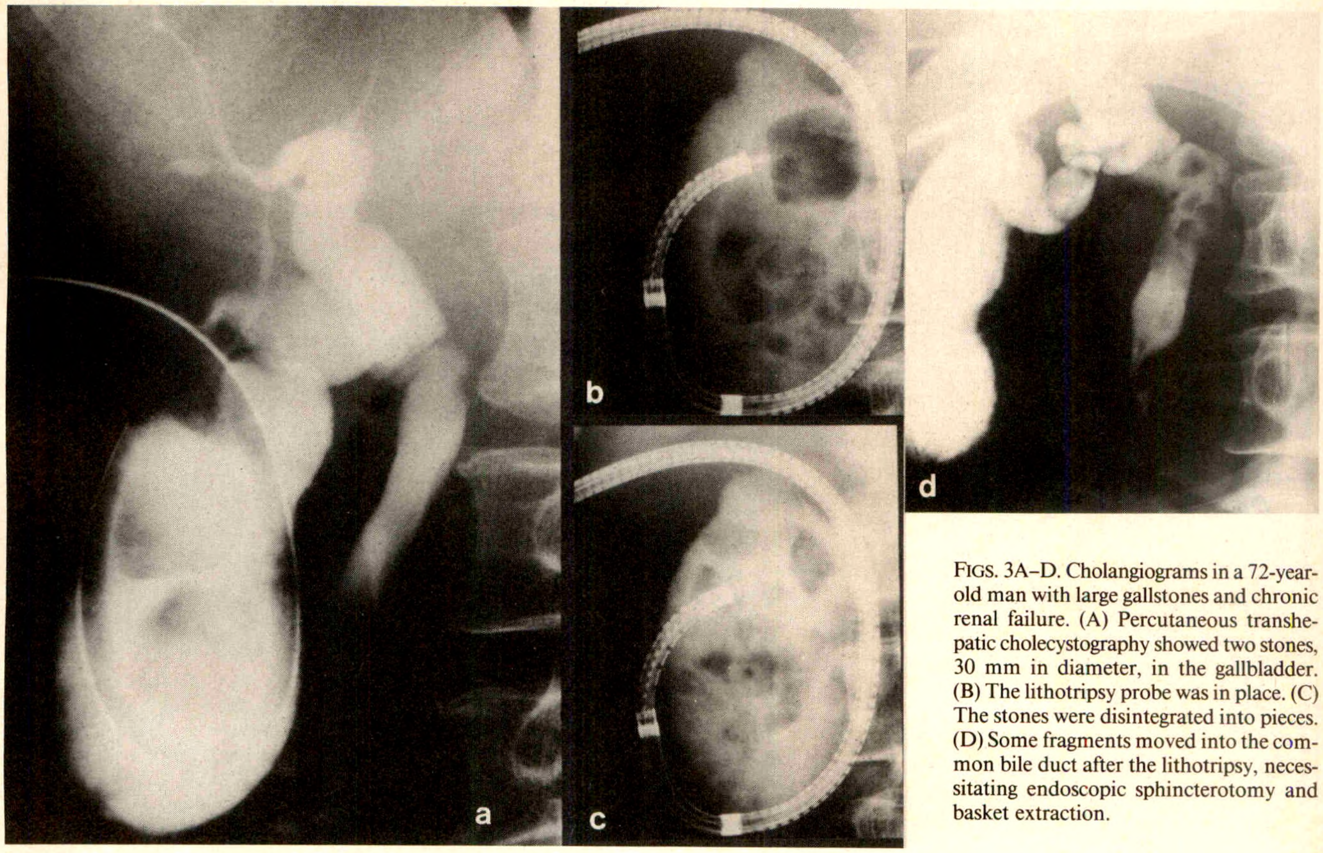
The objective lens at the tip of the choledochoscope was damaged by the shock wave in one of the 51 sessions of lithotripsy. The damage occurred when a large stone impacted in the left hepatic duct was fragmented through the right intercostal approach. It was extremely difficult to keep a sufficient distance between the tip of the choledochoscope and the stone.

TABLE 4. *Number of Choledochoscopic Sessions and Length from Biliary Catheterization to Completion of Lithotomy*

Indications	Number of Sessions*	Biliary Catheterization to Completion of Lithotomy (Days)*
Common duct stones	3.2 ± 1.2	28 ± 6
Gallbladder stones	5.2 ± 2.9	42 ± 14
Intrahepatic stones	6.0 ± 2.6	50 ± 12
Overall	4.5 ± 2.5	40 ± 12

* Mean ± SD.

Twenty-seven patients (choledocholithiasis, 12; cholecystolithiasis, 9; hepatolithiasis, 6) more than 1 year after choledochoscopic lithotripsy were followed by telephone interview. The follow-up period was up to 36 months with a mean of 20.8 ± 8.9 months. Twenty-four of these patients were asymptomatic and two patients were dead. The two death were not related to the lithotripsy procedure. One of the two patients who had hepatolithiasis and biliary cirrhosis secondary to bile duct injury at a previous operation died of hepatic coma and gastrointestinal



FIGS. 3A–D. Cholangiograms in a 72-year-old man with large gallstones and chronic renal failure. (A) Percutaneous transhepatic cholecystography showed two stones, 30 mm in diameter, in the gallbladder. (B) The lithotripsy probe was in place. (C) The stones were disintegrated into pieces. (D) Some fragments moved into the common bile duct after the lithotripsy, necessitating endoscopic sphincterotomy and basket extraction.

bleeding 7 months after lithotripsy and lithotomy. The other patient with obsolete myocardial infarction died of another attack of myocardial infarction 4 months after lithotripsy. Only one of the 27 patients was symptomatic at the follow-up interview. This patient had lithotripsy for the treatment of choledocholithiasis. Computed tomography revealed stones in the left intrahepatic duct that were missed at the time of lithotripsy. Echography performed regularly as a follow-up study for nine patients of cholecystolithiasis revealed new formation of debris in the gallbladder in only one patient 10 months after lithotripsy. Ursodesoxycholic acid and hymecromone were given to this patient for 2 months, which resulted in disappearance of the debris.

Discussion

As described in this report, the use of electrohydraulic lithotripsy either *via* the percutaneous transhepatic route or through the T-tube track has enabled us to remove stones from the common bile duct, intrahepatic ducts, and even the gallbladder. Even large immobile stones were successfully removed after fragmentation once the stones were localized under direct vision by choledochoscopy. The success or failure did not depend on the nature of the stones; even hard, calcified cholesterol stones could be fragmented.

Removal of large stones from the biliary tract has been a challenge for percutaneous choledochoscopic lithotomy. We previously dilated the PTBD tract up to 26 French size to extract a stone of 8 mm in diameter,[9] but the dilatation was associated with considerable pain. Although several types of forceps have been devised, forceps lithotomy has been time-consuming and not always successful.[10] Presence of bile duct stricture may prohibit the efficient use of the forceps. YAG laser has been used during choledochoscopy;[11,12] however current laser lithotripsy has many disadvantages. Lasers do not crush a cholesterol stone satisfactorily, the equipment is expensive, laser delivery needs a water-supplying system, and a quartz fiber to transmit the laser beam is too fragile to be manipulated easily through a choledochoscope and too stiff to be used in small tortuous bile ducts. Electrohydraulic lithotripsy is not associated with any of these drawbacks.

As shown by the number of choledochoscopy sessions and period of time for complete lithotomy, common bile duct stones were most easily removed, chiefly because the common bile duct was straight, allowing easy choledochoscopic access to the stones, and the number of stones was small. Most of the patients had all their stones eliminated in three sessions; 1 for lithotripsy, 1 for extraction of the fragments, and 1 for confirmation of complete clearance of the fragments. This method will be quite an addition to the treatment of common bile duct stones and is the choice in cases of large or impacted stones that are not removable by EST.

Previously we reported usefulness of choledochoscopic electrohydraulic lithotripsy for the treatment of intrahepatic stones.[8] This seems to be the first choice of the treatment in patients who are poor surgical risks. Furthermore choledochoscopic lithotomy before surgery may also be justified even in patients without any risk factors.[13] An appropriate operative procedure for the treatment of hepatolithiasis should be selected on the basis of anatomical location of bile duct stricture often associated with this disease. This can be achieved more accurately after complete removal of the intrahepatic stones because bile duct stricture tends to be improved after removal of the stones. The combination of choledochoscopic lithotomy and electrohydraulic lithotripsy would allow for quick removal of the stones before the surgical procedure is planned.

Cholecystectomy is a relatively safe method for the treatment of stones in the gallbladder. However it carries some risk when the procedure is to be done in high-risk patients. A variety of alternatives such as medical or chemical dissolution and extracorporeal shock wave lithotripsy are now under investigation, but none of them has yet proved satisfactory.[6,7] With the combined use of percutaneous transhepatic cholecystoscopy[14] and electrohydraulic lithotripsy, we treated poor-risk patients with gallstones or a so-called confluence stone. The confluence stone is an extremely complicated condition in which a stone lodged right at the junction of the cystic duct and common bile duct causes cholangitis and jaundice. A PTBD reduces jaundice and at the same time provides a route for choledochoscopic lithotripsy and lithotomy (Fig. 1).

A major drawback of choledochoscopic lithotripsy is that it takes at least 3 weeks for dilatation and maturation of the percutaneous track before choledochoscopy is attempted. To shorten the period for establishing the percutaneous track, we are now conducting a new trial in which PTBD and dilatation are performed on the same day under epidural anesthesia and choledochoscopy is started in a week using an overtube to protect the sinus tract. The results of this trial will be the subject of a future report. Fragmentation and removal of the stones in the gallbladder needs even a longer period than stones in the common bile duct and intrahepatic ducts because the gallstones are usually hard, large, and multiple. Additional problems associated with lithotripsy of the gallstones are that fragments after lithotripsy may migrate into the common bile duct and require EST to remove them, and that gallstones may reform after a certain period of time, as seen in one of our patients 10 months after lithotomy. These problems must await future investigation to be resolved.

Complications encountered in this series include minor bleeding and shivering chills. The bleeding occurred due to friction of the ductal wall by the sharp edge of the tip of the lithotripsy probe. Therefore the metal ring at the probe tip has been refined into smoother shape, leading to a decrease in the incidence of such bleeding. The choledochoscopic view was often blurred by blood, dispersed fragments, and bubbles. The use of the large-caliber choledochoscope was helpful to keep the view clear due to the larger channel for perfusion. However instillation of a large amount of saline into the biliary tract might cause undesirable elevation of ductal pressure. In fact, shivering chills and fever probably due to cholangiovenous reflux occurred in three of our patients. Development of a choledochoscope with two catheter channels for perfusion and suction would be mandatory to overcome this problem.

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PARENTERAL POWER IN ORAL FORM:

THE POWER TO ERADICATE.*

Cipro®

(ciprofloxacin HCl/Miles)

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* Achieves 97% favorable clinical response (resolution + improvement) of infections due to susceptible strains of indicated pathogens. See indicated organisms in prescribing information.

THE POWER TO ERADICATE* IN UTI.

In the tissues and fluid — that's where an antimicrobial has to perform in urinary tract infections and that's where Cipro® excels.

Cipro® has achieved outstanding clinical response in infections including complicated and uncomplicated UTI, prostatitis, pyelonephritis, cystitis, urethritis, epididymitis, and asymptomatic bacteriuria: **97%** were cured or improved.[1*†]

In vitro, Cipro® outpowers clinically important uropathogens, including many missed by other agents.[2*] Concentrating more killing power in vitro than norfloxacin, Cipro® delivers 4 to 8 times more activity against gram-negative bacteria[3‡]—plus achieves high concentrations in urine and prostate tissue.[2,4,5*§]

If all that weren't enough, the cost of therapy with Cipro® is comparable with other agents—including norfloxacin[6]—and it's generally well tolerated.

NOTES: Concurrent administration of ciprofloxacin with theophylline may lead to elevated plasma concentrations of theophylline and prolongation of its elimination half-life. This may result in increased risk of theophylline-related adverse reactions. If concomitant use cannot be avoided, plasma levels of theophylline should be monitored and dosage adjustments made as appropriate.

Antacids containing magnesium hydroxide or aluminum hydroxide interfere with the absorption of ciprofloxacin, resulting in serum and urine levels lower than desired; concurrent administration of these agents with ciprofloxacin should be avoided.

A history of hypersensitivity to ciprofloxacin is a contraindication to its use. A history of hypersensitivity to other quinolones may also contraindicate the use of ciprofloxacin.

CIPRO® SHOULD NOT BE USED IN CHILDREN, ADOLESCENTS, OR PREGNANT WOMEN.

The eradicator.*

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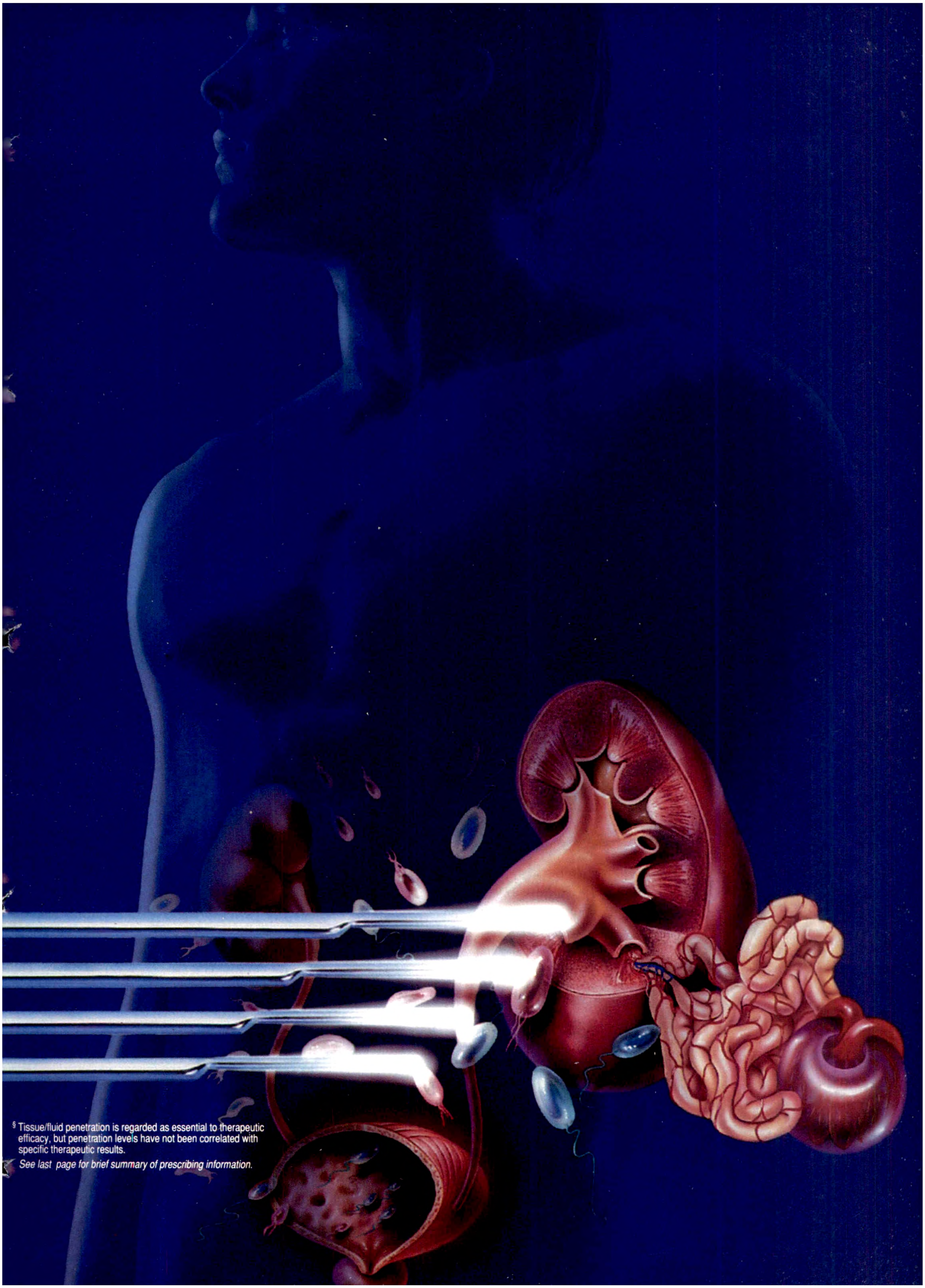
* **Achieves 97% favorable clinical response (resolution + improvement) of infections due to susceptible strains of indicated pathogens. See indicated organisms in prescribing information.**

† Clinical response data derived from a pool of studies conducted by investigators who may have used different criteria to define "resolution" plus "improvem

‡ In vitro activity does not necessarily imply a correlation with in vivo results.



§ Tissue/fluid penetration is regarded as essential to therapeutic efficacy, but penetration levels have not been correlated with specific therapeutic results.

See last page for brief summary of prescribing information.

Cipro® TABLETS

(ciprofloxacin HCl/Miles)

THE POWER TO ERADICATE* IN UTI.

CIPRO® TABLETS
(ciprofloxacin HCl/Miles)

BRIEF SUMMARY
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INDICATIONS AND USAGE

Cipro® is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below:

Lower Respiratory Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, and *Streptococcus pneumoniae*.

Skin and Skin Structure Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Proteus mirabilis*, *Proteus vulgaris*, *Providencia stuartii*, *Morganella morganii*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Streptococcus pyogenes*.

Bone and Joint Infections caused by *Enterobacter cloacae*, *Serratia marcescens*, and *Pseudomonas aeruginosa*.

Urinary Tract Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Serratia marcescens*, *Proteus mirabilis*, *Providencia rettgeri*, *Morganella morganii*, *Citrobacter diversus*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Staphylococcus epidermidis*, and *Streptococcus faecalis*.

Infectious Diarrhea caused by *Escherichia coli* (enterotoxigenic strains), *Campylobacter jejuni*, *Shigella flexneri*,* and *Shigella sonnei** when antibacterial therapy is indicated.

*Efficacy for this organism in this organ system was studied in fewer than 10 infections.

CONTRAINDICATIONS

A history of hypersensitivity to ciprofloxacin is a contraindication to its use. A history of hypersensitivity to other quinolones may also contraindicate the use of ciprofloxacin.

WARNINGS

CIPROFLOXACIN SHOULD NOT BE USED IN CHILDREN, ADOLESCENTS, OR PREGNANT WOMEN. The oral administration of ciprofloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related drugs such as nalidixic acid, cinoxacin, and norfloxacin also produced erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species (SEE ANIMAL PHARMACOLOGY SECTION IN FULL PRESCRIBING INFORMATION).

PRECAUTIONS

General: As with other quinolones, ciprofloxacin may cause central nervous system (CNS) stimulation, which may lead to tremor, restlessness, lightheadedness, confusion, and rarely to hallucinations or convulsive seizures. Therefore, ciprofloxacin should be used with caution in patients with known or suspected CNS disorders, such as severe cerebral arteriosclerosis or epilepsy, or other factors which predispose to seizures (SEE ADVERSE REACTIONS).

Anaphylactic reactions following the first dose have been reported in patients receiving therapy with quinolones. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial edema, dyspnea, urticaria, and itching. Only a few patients had a history of hypersensitivity reaction. Anaphylactic reactions may require epinephrine and other emergency measures. Ciprofloxacin should be discontinued at the first sign of hypersensitivity or allergy.

Severe hypersensitivity reactions characterized by rash, fever, eosinophilia, jaundice, and hepatic necrosis with fatal outcome have been reported rarely (less than one per million prescriptions) in patients receiving ciprofloxacin along with other drugs. The possibility that these reactions were related to ciprofloxacin cannot be excluded. Ciprofloxacin should be discontinued at the first appearance of a skin rash or any sign of other hypersensitivity reaction.

Crystals of ciprofloxacin have been observed rarely in the urine of human subjects but more frequently in the urine of laboratory animals (SEE ANIMAL PHARMACOLOGY SECTION IN FULL PRESCRIBING INFORMATION). Crystalluria related to ciprofloxacin has been reported only rarely in man, because human urine is usually acidic. Patients receiving ciprofloxacin should be well hydrated, and alkalinity of the urine should be avoided. The recommended daily dose should not be exceeded.

Alteration of the dosage regimen is necessary for patients with impairment of renal function (SEE DOSAGE AND ADMINISTRATION).

As with any potent drug, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic function, is advisable during prolonged therapy.

Drug Interactions: As with other quinolones, concurrent administration of ciprofloxacin with theophylline may lead to elevated plasma concentrations of theophylline and prolongation of its elimination half-life. This may result in increased risk of theophylline-related adverse reactions. If concomitant use cannot be avoided, plasma levels of theophylline should be monitored and dosage adjustments made as appropriate.

Quinolones, including ciprofloxacin, have also been shown to interfere with the metabolism of caffeine. This may lead to reduced clearance of caffeine and a prolongation of its plasma half-life.

Antacids containing magnesium hydroxide or aluminum hydroxide may interfere with the absorption of ciprofloxacin resulting in serum and urine levels lower than desired; concurrent administration of these agents with ciprofloxacin should be avoided.

Concomitant administration of the nonsteroidal anti-inflammatory drug fenbufen with a quinolone has been reported to increase the risk of CNS stimulation and convulsive seizures.

Probenecid interferes with the renal tubular secretion of ciprofloxacin and produces an increase in the level of ciprofloxacin in the serum. This should be considered if patients are receiving both drugs concomitantly.

As with other broad-spectrum antibiotics, prolonged use of ciprofloxacin may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition and microbial susceptibility testing is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Information for Patients: Patients should be advised that ciprofloxacin may be taken with or without meals. The preferred time of dosing is two hours after a meal. Patients should also be advised to drink fluids liberally and not take antacids containing magnesium or aluminum.

Patients should be advised that ciprofloxacin may be associated with hypersensitivity reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash or other allergic reaction.

Ciprofloxacin may cause dizziness or lightheadedness; therefore patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or coordination.

Patients should be advised that ciprofloxacin may increase the effects of theophylline and caffeine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Eight in vitro mutagenicity tests have been conducted with ciprofloxacin and the test results are listed below:

- Salmonella/Microsome Test (Negative)
- *E. coli* DNA Repair Assay (Negative)
- Mouse Lymphoma Cell Forward Mutation Assay (Positive)
- Chinese Hamster V_{79} Cell HGPRT Test (Negative)
- Syrian Hamster Embryo Cell Transformation Assay (Negative)
- *Saccharomyces cerevisiae* Point Mutation Assay (Negative)
- *Saccharomyces cerevisiae* Mitotic Crossover and Gene Conversion Assay (Negative)
- Rat Hepatocyte DNA Repair Assay (Positive)

Thus, two of the eight tests were positive, but the results of the following three *in vivo* test systems gave negative results:

- Rat Hepatocyte DNA Repair Assay
- Micronucleus Test (Mice)
- Dominant Lethal Test (Mice)

Long-term carcinogenicity studies in rats and mice have been completed. After daily oral dosing for up to 2 years, there is no evidence that ciprofloxacin had any carcinogenic or tumorigenic effects in these species.

Pregnancy—Pregnancy Category C: Reproduction studies have been performed in rats and mice at doses up to 6 times the usual daily human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ciprofloxacin. In rabbits, as with most antimicrobial agents, ciprofloxacin (30 and 100 mg/kg orally) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion. No teratogenicity was observed at either dose. After intravenous administration, at doses up to 20 mg/kg, no maternal toxicity was produced, and no embryotoxicity or teratogenicity was observed. There are, however, no adequate and well-controlled studies in pregnant women. SINCE CIPROFLOXACIN, LIKE OTHER DRUGS IN ITS CLASS, CAUSES ARTHROPATHY IN IMMATURE ANIMALS, IT SHOULD NOT BE USED IN PREGNANT WOMEN (SEE WARNINGS).

Nursing Mothers: It is not known whether ciprofloxacin is excreted in human milk; however, it is known that ciprofloxacin is excreted in the milk of lactating rats and that other drugs of this class are excreted in human milk. Because of this and because of the potential for serious adverse reactions from ciprofloxacin in nursing infants, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Patients under the age of 18 were not included in the clinical trials of ciprofloxacin because ciprofloxacin as well as other quinolones causes arthropathy in immature animals. Ciprofloxacin should not be used in children or adolescents (SEE WARNINGS).

ADVERSE REACTIONS

Ciprofloxacin is generally well tolerated. During clinical investigation, 2,799 patients received 2,868 courses of the drug. Adverse events that were considered likely to be drug related occurred in 7.3% of courses, possibly related in 9.2%, and remotely related in 3.0%. Ciprofloxacin was discontinued because of an adverse event in 3.5% of courses, primarily involving the gastrointestinal system (1.5%), skin (0.6%), and central nervous system (0.4%). Those events typical of quinolones are italicized.

The most frequently reported events, drug related or not, were *nausea* (5.2%), *diarrhea* (2.3%), *vomiting* (2.0%), *abdominal pain/discomfort* (1.7%), *headache* (1.2%), *restlessness* (1.1%), and *rash* (1.1%).

Additional events that occurred in less than 1% of ciprofloxacin courses are listed below.

GASTROINTESTINAL: *(See above)*, painful oral mucosa, oral candidiasis, dysphagia, intestinal perforation, gastrointestinal bleeding.

CENTRAL NERVOUS SYSTEM: *(See above), dizziness, lightheadedness, insomnia, nightmares, hallucinations, manic reaction, irritability, tremor, ataxia, convulsive seizures, lethargy, drowsiness, weakness, malaise, anorexia, phobia, depersonalization, depression, paresthesia.*

SKIN/HYPERSENSITIVITY: *(See above), pruritus, urticaria, photosensitivity, flushing, fever, chills, angioedema, edema of the face, neck, lips, conjunctivae or hands*, cutaneous candidiasis, hyperpigmentation, erythema nodosum.

Allergic reactions ranging from urticaria to anaphylactic reactions have been reported (SEE PRECAUTIONS).

SPECIAL SENSES: *blurred vision, disturbed vision (change in color perception, overbrightness of lights), decreased visual acuity, diplopia, eye pain, tinnitus, hearing loss, bad taste.*

MUSCULOSKELETAL: *joint or back pain, joint stiffness*, achiness, neck or chest pain, flare-up of gout.

RENAL/UROGENITAL: *interstitial nephritis, nephritis, renal failure*, polyuria, urinary retention, urethral bleeding, vaginitis, acidosis.

CARDIOVASCULAR: palpitations, atrial flutter, ventricular ectopy, syncope, hypertension, angina pectoris, myocardial infarction, cardiopulmonary arrest, cerebral thrombosis.

RESPIRATORY: epistaxis, laryngeal or pulmonary edema, hiccough, hemoptysis, dyspnea, bronchospasm, pulmonary embolism.

Most of the adverse events reported were described as only mild or moderate in severity, abated soon after the drug was discontinued, and required no treatment.

In several instances, nausea, vomiting, tremor, restlessness, agitation, or palpitations were judged by investigators to be related to elevated plasma levels of theophylline possibly as a result of a drug interaction with ciprofloxacin.

Other adverse events reported in the postmarketing phase include anaphylactoid reactions, Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, hepatic necrosis, postural hypotension, possible exacerbation of myasthenia gravis, confusion, dysphasia, nystagmus, pseudomembranous colitis, dyspepsia, flatulence, and constipation. Also reported were agranulocytosis; elevation of serum triglycerides, serum cholesterol, blood glucose, serum potassium; prolongation of prothrombin time; albuminuria; candiduria, vaginal candidiasis; and renal calculi (SEE PRECAUTIONS).

Adverse Laboratory Changes: Changes in laboratory parameters listed as adverse events without regard to drug relationship:

Hepatic—Elevations of: ALT (SGPT) (1.9%), AST (SGOT) (1.7%), alkaline phosphatase (0.8%), LDH (0.4%), serum bilirubin (0.3%).

Cholestatic jaundice has been reported.

Hematologic—Eosinophilia (0.6%), leukopenia (0.4%), decreased blood platelets (0.1%), elevated blood platelets (0.1%), pancytopenia (0.1%).

Renal—Elevations of: Serum creatinine (1.1%), BUN (0.9%).

CRYSTALLURIA, CYLINDRURIA, AND HEMATURIA HAVE BEEN REPORTED.

Other changes occurring in less than 0.1% of courses were: Elevation of serum gammaglutamyl transferase, elevation of serum amylase, reduction in blood glucose, elevated uric acid, decrease in hemoglobin, anemia, bleeding diathesis, increase in blood monocytes, and leukocytosis.

OVERDOSAGE

Information on overdosage in humans is not available. In the event of acute overdosage, the stomach should be emptied by inducing vomiting or by gastric lavage. The patient should be carefully observed and given supportive treatment. Adequate hydration must be maintained. Only a small amount of ciprofloxacin (<10%) is removed from the body after hemodialysis or peritoneal dialysis.

DOSAGE AND ADMINISTRATION

The usual adult dosage for patients with urinary tract infections is 250 mg every 12 hours. For patients with complicated infections caused by organisms not highly susceptible, 500 mg may be administered every 12 hours.

Lower respiratory tract infections, skin and skin structure infections, and bone and joint infections may be treated with 500 mg every 12 hours. For more severe or complicated infections, a dosage of 750 mg may be given every 12 hours.

The recommended dosage for infectious diarrhea is 500 mg every 12 hours.

In patients with renal impairment, some modification of dosage is recommended (SEE DOSAGE AND ADMINISTRATION SECTION IN FULL PRESCRIBING INFORMATION).

HOW SUPPLIED

Cipro® (ciprofloxacin HCl/Miles) is available as tablets of 250 mg, 500 mg, and 750 mg in bottles of 50, and in Unit-Dose packages of 100 (SEE FULL PRESCRIBING INFORMATION FOR COMPLETE DESCRIPTION).

References: 1. Data on file, Miles Inc, Pharmaceutical Division. **2.** *Physicians' Desk Reference®*. 43rd ed. Oradell, NJ: Medical Economics Co Inc; 1989:891, 1376, 1441, 1486, 1724, 1779. **3.** Barry AL, et al. Antibacterial activities of ciprofloxacin, norfloxacin, oxolinic acid, cinoxacin, and nalidixic acid. *Antimicrob Agents Chemother*. 1984;25:633-637. **4.** Borner K, et al. Pharmacokinetics of ciprofloxacin in healthy volunteers after oral and intravenous administration. *Eur J Clin Microbiol*. 1986;5:179-186. **5.** Gombert ME, et al. Levels of ciprofloxacin in prostatic tissue of patients undergoing prostatectomy. *Rev Infect Dis*. 1988;10(suppl 1):S169. **6.** *Medi-Span® Hospital Formulary Pricing Guide*. June 1989:9,35.

***Achieves 97% favorable clinical response (resolution + improvement) of infections due to susceptible strains of indicated pathogens. See indicated organisms in prescribing information.**

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Belsey and Nissen Operations for Gastresophageal Reflux

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From 1972 to 1985, 37 consecutive patients underwent primary Belsey repair and 40 consecutive patients underwent primary Nissen fundoplication because of reflux disease. The operative procedures were performed by a single surgeon in each group. For the purpose of comparison, both groups were divided into two subsets: (1) patients with proved reflux, and (2) patients with different indications. The first subset consisted of 30 patients in the Belsey series and 32 in the Nissen series. The remaining patients were included in the second subset. One death occurred in the Belsey series; morbidity consisted of minor pulmonary complications in the Belsey series (10.8%) and spleen injuries requiring splenectomy (5%) in the Nissen series. In patients with proved reflux good-to-excellent results were achieved in 89.3% of subjects of the Belsey series and 86.6% of patients of the Nissen group. The failures rates were 7.1% and 10%, respectively. Inability to vomit and/or belch was reported in 7.1% of patients with proved reflux of the Belsey group and 10% of patients with proved reflux of the Nissen group. In patients with different indications there were no failures after either operation. Finally 82.2% of subjects in the Belsey group and 73.3% of patients in the Nissen group declared that they were satisfied with the operative results. In conclusion the Belsey and the Nissen procedures are equally able to achieve long-term control of reflux disease in comparable groups of patients. Failures and gastrointestinal symptoms are equally frequent after either procedure and do not affect the overall patient acceptance of antireflux surgery.

THE OPERATIVE CORRECTION of gastroesophageal reflux (GER) has progressed from early attempts to repair a hernia to the current goal of constructing a competent antireflux mechanism. However disagreement exists as to which approach and sphincter-enhancing procedure are best. Although experimental studies[1] suggest that Nissen fundoplication is superior to the Belsey procedure in the control of reflux, controversial clinical results have been reported by several authors.[2-6] This observation supports the need for further studies that compare consecutive series of subjects with the same surgical indications and regular follow-up.

This study was undertaken to compare the clinical results of 37 consecutive primary Belsey repairs and 40 consecutive primary Nissen fundoplications performed in two surgical units by the same surgeons, over the same period, and with a minimum follow-up of 2 years.

Patient Population

Between January 1972 and December 1987, 729 patients were referred to the Esophageal Laboratory of the unit adopting the Belsey technique because of reflux symptoms. From 1972 to 1977, 29 of 140 patients observed underwent surgery because of reflux disease (21%). From 1978, 24-hour pH monitoring of the esophagus was available for patients work-up and more effective antireflux drugs were adopted on a routine basis. Using this policy, patients were more strictly selected. In the last 10 years the average need for antireflux surgery was 11% (Fig. 1), decreasing from 14% in 1981 to 3% in 1987. Overall 63 consecutive patients were submitted to surgical treatment from January 1972 to December 1985. In the same years, 50 patients in the other unit were operated on for similar reflux problems (for this second unit, data concerning the overall population observed are not available).

For the purpose of comparison, the population of patients submitted to antireflux procedures was broken down into two subsets: group 1: subjects with proved reflux (when ulcerative/erosive esophagitis was present or minor endoscopic lesions were associated with a positive Standard Acid Reflux Test or positive 24-hour pH monitoring of the distal esophagus); group 2: subjects with different indications (absence of esophagitis or negative pH test

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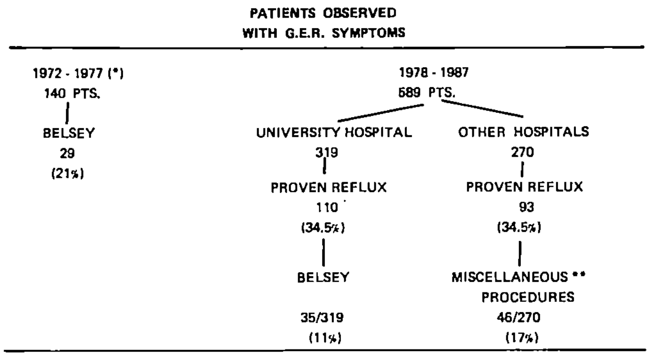

(*) Data on the overall number of pts. with proven reflux are not available from 1972 to 1977.
(**) Nissen, Belsey, Toupet, Dor, Angelchik.

FIG. 1. Outcome of patients with reflux symptoms observed in the esophageal laboratory of the I Department of Surgery from 1972 to 1987.

with only symptoms and/or roentegenographic findings supporting the diagnosis of GER). These patients belong to the earlier experience of both groups and, therefore, their results are presented separately.

Subjects with peptic stenoses, previous esophageal surgery, scleroderma, paraesophageal hernias, and patients operated on by others were excluded from the study. Therefore the population studied consisted of 37 patients submitted to the Belsey procedure and 40 to Nissen fundoplication. Table 1 shows the indications for surgery and reasons for exclusion of subjects in both groups.

There were 18 women and 19 men in the Belsey group and 26 women and 14 men in the Nissen group. The mean age was 47 years (range, 21 to 71 years) in the Belsey group and 51 years (range, 28 to 68 years) in the Nissen group.

Heartburn and regurgitation were the most prominent symptoms, with an incidence of 86% and 90% in patients with proved reflux who underwent the Belsey procedure and 100% and 90% in patients with proved reflux submitted to the Nissen fundoplication. Esophageal symptoms were less frequently observed in patients with different indications (Fig. 2).

The mean duration of symptoms was 89 months (range, 3 to 276 months) in the Belsey group and 112 months (range, 12 to 240 months) in the Nissen group.

On upper gastrointestinal roentegenographic barium studies a hiatal hernia was found in 24 or 80% of patients with proved reflux of the Belsey group and in 28 or 87.5% of patients with proved reflux of the Nissen group.

In addition a hiatal hernia was present in four patients with different indications of the Belsey group and in 3 patients with different indications of the Nissen group.

An associate disease was documented in four patients with proved reflux of the Belsey group (duodenitis endoscopically proved) and in six patients with proved reflux of the Nissen group (gallbladder stones in two patients, duodenal ulcer, gastric ulcer, colon diverticulosis, and duodenal diverticulum, in four additional patients). At the time of the Nissen fundoplication, two cholecystectomies and one selective vagotomy plus pyloroplasty and a left colectomy were added to the antireflux procedure. There were no associate diseases in patients with different indications who underwent the Belsey procedure; in patients with different indications submitted to the Nissen fundoplication, four patients had associate diseases (gallbladder stones in two patients, colon cancer and colon diverticulosis in two others). At the time of the Nissen fundoplication, two cholecystectomies and two left colectomies were added.

The clinical indication for the antireflux repair was the persistence of symptoms in all patients after at least 3 months of adequate medical treatment. This included dietary manipulation, postural therapy, and a variety of drug

TABLE 1. *Gastroesophageal Reflux Belsey—Nissen Comparison (1972–1985)*

Indication	Belsey (Pts.)	Nissen (Pts.)
Ulcerative/erosive esophagitis	15 (40.5%)	19 (47.5%)
Hyperemic esophagitis + positive pH-Test	9 (24.3%)	9 (22.5%)
Absent/esophagitis + positive pH-Test	6 (16.2%)	4 (10.0%)
Total proved reflux	30 (81.1%)	32 (80.0%)
Different indication	7 (18.9%)	8 (20.0%)
Upper G.I. bleeding	2	2
Aspiration	1	3
G.E.R. symptoms	4	3
Total patients entered the study	37 (100%)	40 (100%)
Reoperations	9	4
Stenoses	6	3
Scleroderma	3	0
Paraesophageal hernia	0	3
Patients excluded from the study	18	10

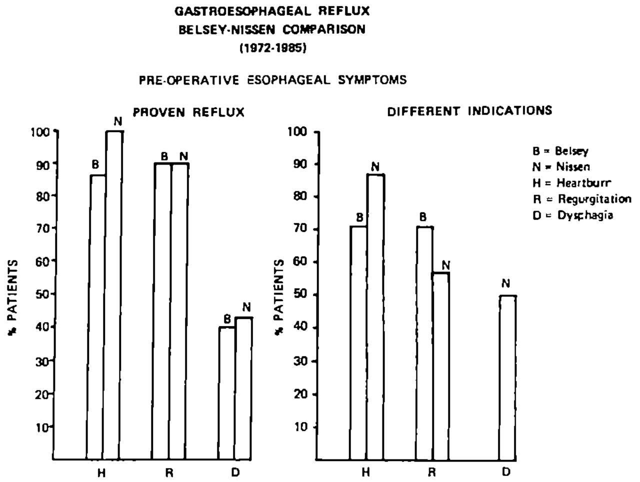

FIG. 2. Incidence and severity of reflux symptoms in patients submitted to Belsey or Nissen fundoplication from 1972 to 1985.

therapies. The clinical evaluation of postoperative symptoms was based on a questionnaire proposed by the authors, with personal interviews with all patients who entered into the study.

In the Belsey group two patients with proved reflux and two with different indications were lost at the follow-up; two patients with proved reflux and one with different indications were lost in the Nissen group.

Therefore a complete follow-up was available in 93.3% of patients with proved reflux and 66.7% of patients with different indications who underwent Belsey repair. In the Nissen group, a complete follow-up was available in 93.8% and 87.5% patients, respectively.

In the Belsey series, two patients with proved reflux died 60 and 89 months after the antireflux surgery of causes unrelated to the previous esophageal disease or surgery.

In the Nissen group there were two unrelated deaths (in patients with proved reflux) 48 and 84 months after esophageal surgery. The follow-up of dead patients was accomplished with interviews to the referring physicians and therefore all of them were included in the study.

The results of the surgical treatment were graded as excellent, good, fair, or failure according to the presence and severity of esophageal symptoms as shown in Table 2.

At the end of the interviews each patient was asked for a personal opinion of the operation, giving a statement as cured, improved, or unimproved.

The whole follow-up study was completed within the 12 months before the preparation of this paper. The mean follow-up of patients with proved reflux was 91 months in the Belsey group and 84 months in the Nissen group. In the group with different indications, the mean follow-up was 122 months in the Belsey series and 102 months in the Nissen series.

Methods

The diagnosis of reflux was based on symptoms, roentegenographic findings, and endoscopy in all patients.

TABLE 2. *Belsey–Nissen Comparison Esophageal Symptoms* Grading*

	Clinical Result	Symptoms Grading
	Excellent	No symptoms
	Good	Occasional† esophageal symptoms
Therapy Required	Fair	One moderate‡ esophageal symptom (requiring medical advice)
	Failure	Two moderate esophageal symptoms or disabling symptoms

* Heartburn, regurgitation, dysphagia, retrosternal pain.

† Occasional symptoms: infrequent, not requiring medical advice and therapy.

‡ Moderate symptoms: requiring medical advice and therapy (occasional to continuous treatment).

TABLE 3. *Gastroesophageal Reflux Belsey–Nissen Comparison (1972–1985); Patients with Proved Reflux; Short-Term Results*

Postoperative Results	Belsey (30 Pts.)	Nissen (32 Pts.)
Operative mortality	—	—
Incidental splenectomy	—	2 (6.2%)
Postop. complications	4 (13.3%)	—
Pleural effusion	2	—
R.L.L. atelectasis	1	—
Pneumonitis	1	—

Manometry was performed in 26 patients in the Belsey group and 27 in the Nissen group, and Standard Acid Reflux Test (SART) in 19 and 33 patients, respectively. 24-hour pH monitoring of the distal esophagus was performed in 21 patiens of the Belsey series and in none of the Nissen series.

Endoscopy

Esophagitis was scored as grade 1 for erythematous and friable mucosa, grade 2 for linear erosions, and grade 3 for ulcerative lesions.

Manometry

Esophageal manometry was performed according to the technique described by Winans and Harris[7] using a single-catheter assembly consisting of three fluid-filled polyethilene tubes bent together.

Twenty-Four-Hour Esophageal pH Monitoring

The examination was performed according to the technique described by Johnson and De Meester[8] with the pH probe placed 5 cm above the upper border of the lower esophageal sphincter.

SART

SART was performed according to the technique previously described.[9]

Results

Patients with Proved Reflux

Short-term results. There were no postoperative deaths after either procedure. Morbidity was 6.2% after the Nissen procedure, consisting of two spleen injuries that required splenectomies at the time of the antireflux surgery. Complications followed the Belsey repair in 13.3% of patients. They were all minor pulmonary problems and none was life-threatening (Table 3).

Long-term results. Table 4 shows the long-term results of the Belsey and Nissen procedures: good-to-excellent results were achieved in 89.3% of subjects of the Belsey series and in 86.6% of the Nissen group. In the Belsey group, recurrent reflux symptoms accounted for all the unsatisfactory results; they appeared 8 years after surgery in the patients with fair results and 1 and 9 years after treatment in patients with failures. Delayed gastric emptying was detected in the first patient, obesity and recurrent hiatal hernia in the second, and nonspecific motor abnormalities of the esophageal body in the third. Medical treatment controlled reflux symptoms in all patients with satisfactory results.

In the Nissen group the only fair result was due to reflux symptoms, dysphagia, and recurrent hiatal hernia due to a slipped fundoplication that appeared 48 months after the antireflux surgery. Symptoms improved with nonoperative therapy needing no additional treatment. A tight wrap and a fundoplication slipped in the chest were the cause of failures in two patiens with obstructing symptoms, appearing in the postoperative period in the first and 2 years after surgery in the second. Reflux symptoms and a disrupted Nissen fundoplication appeared 36 months after surgery in the third patient. Only this last patient underwent a reoperation, which consisted of a redo Nissen, with good result. Both patients with obstructive symptoms refused any further treatment. A more detailed analysis of the frequency and type of residual or recurrent esophageal symptoms, after either procedure, is shown in Figure 3. These symptoms were present in 9 patients (32%) of the Belsey group (6 good, 1 fair, 2 failures) and 14 patients (46.6%) of the Nissen series (10 good, 1 fair, 3 failures). Heartburn was more frequently observed after the Belsey procedure, and dysphagia and retrosternal pain were more common after the Nissen fundoplication.

Late gastrointestinal symptoms: gastrointestinal symptoms were occasionally present in 18 of 28 patients (64.3%) of the Belsey group and in 19 of 30 patients (63.3%) of the Nissen group. The inability to vomit and/or belch was present in two patients of the Belsey group and in three of the Nissen group (Table 5).

Seven of 28 patients of the Belsey group (24.5%) complained of occasional incisional pain needing no therapy, while no patients in the Nissen series suffered such pain.

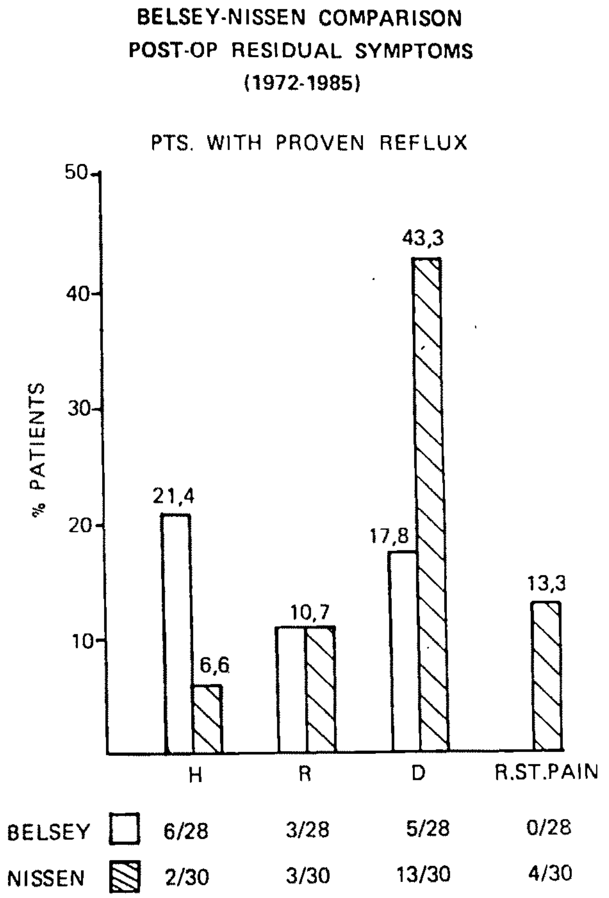

FIG. 3. Postoperative presence of esophageal symptoms in patients with proved reflux submitted to Belsey or Nissen procedures from 1972 to 1985.

Finally 23 patients of 28 (82.2%) of the Belsey group and 22 of 30 patients (73.3%) of the Nissen group declared that they were satisfied with the operative results (Table 6).

Patients with Different Indications

Short-term results. The only postoperative death occurred in the Belsey group (14.5%) because of sepsis. There were no further complications after either procedure (Table 7).

Long-term results. Good-to-excellent results were achieved in 100% of patients in the Belsey and Nissen groups. There were no failures (Table 8).

TABLE 4. *Gastroesophageal Reflux Belsey–Nissen Comparison (1972–1985); Long-Term Results; Pts. with Proved Reflux*

Results	Belsey (30 Pts.)	Nissen (32 Pts.)
Lost	2 (6.7%)	2 (6.2%)
Excellent results	19/28 (67.9%)	16/30 (53.3%)
	89.3%	86.5%
Good results	6/28 (21.4%)	10/30 (33.3%)
Fair results	1/28 (3.6%)	1/30 (3.3%)
Failures	2/28 (7.1%)	3/30 (10.0%)

TABLE 5. *Gastroesophageal Reflux Belsey–Nissen Comparison (1972–1985) Postop. G.I. Symptoms Pts. with Proved Reflux*

Symptoms	Belsey 18/28 (64.3%)	Nissen 19/30 (63.3%)
Postprandial fullness/early satiety	8/28 (28.6%)	12/30 (40%)
Nausea/vomiting	*5/28 (17.9%)	1/30 (3.3%)
Epigastric pain/pyrosis	†4/28 (14.3%)	5/30 (16.7%)
Inability belch/vomit	2/28 (7.1%)	3/30 (10%)

* 2 pts. with preop. duodenitis.
† 3 pts. with preop. duodenitis.

TABLE 6. *Gastroesophageal Reflux Belsey–Nissen Comparison (1972–1985) Patients with Proved Reflux Patient Opinion*

Opinion	Belsey (28 Pts.)	Nissen (30 Pts.)
Cured	15 (53.6%)	7 (23.3%)
	82.2%	73.3%
Improved	8 (28.6%)	15 (50%)
Unimproved/worsened	2 (7.1%)	4 (13.3%)
Unknown*	3 (10.7%)	4 (13.3%)

* Dead patients and patients who did not give an opinion.

Figure 4 shows in detail the residual or recurrent esophageal symptoms after Belsey and Nissen repairs.

Late gastrointestinal symptoms. Three of four patients of the Belsey group and five of seven patients of the Nissen group complained of these symptoms. The inability to vomit or belch was present in one patient (25%) submitted to the Belsey procedure (Table 9). Two patients in the Belsey group (50%) complained of occasional incisional pain while no patients in the Nissen series suffered such pain.

Finally 100% of patients after the Belsey repair or the Nissen fundoplication were satisfied with the results of the performed operation (Table 10).

Discussion

This comparison of two different antireflux procedures was undertaken on the basis of the following criteria:

(1) The procedures were performed on consecutive series of patients operated on over the same period.

(2) In each group a single surgeon was involved in the treatment of all patients.

(3) Only primary repairs were included in the study group.

(4) A complete follow-up was available in 90% of subjects entered into the study and was based on a common questionnaire, proposed to each patient, with personal interviews conducted by the same physicians.

(5) Clinical comparisons were performed between subsets of patients with similar preoperative assessment and clinical/diagnostic situations.

Therefore our study, although retrospective and clinical, allows us some observations and comments.

Intraoperative and postoperative morbidity, after the Belsey MKIV procedure, has been reported with ranges from 0% to 40% and included a variety of complications, such as visceral injury, bleeding, wound dehiscence, pneumonia, atelectasis, empyema, and pulmonary embolus.[2,3,10,11]

After Nissen fundoplication the reported morbidity rates range from 9% to 33%.[2–4,10,12–14] Complications are similar to those described after the Belsey repair but visceral injuries, specifically spleen damage, are more commonly observed.[10,15,16] In our study the only death occurred in the Belsey group as a result of sepsis.

The overall incidence of postoperative complications was low and not life-threatening after either procedure

TABLE 7. *Gastroesophageal Reflux Belsey–Nissen Comparison (1972–1985); Patients with Different Indication; Short-Term Results*

Postoperative Results	Belsey (7 Pts.)	Nissen (8 Pts.)
Operative Mortality	1 (14.3%)	—
Incidental Splenectomy	—	—
Postop. Complications	—	—

TABLE 8. *Gastroesophageal Reflux Belsey–Nissen Comparison (1972–1985); Pts. with Different Indications; Long-Term Results*

Results	Belsey (6 Pts.)	Nissen (8 Pts.)
Lost	2 (33.3%)	1 (12.5%)
Excellent Results	2/4 (50%)	7/7 (100%)
Good Results	2/4 (50%)	—
Fair Results	—	—
Failures	—	—

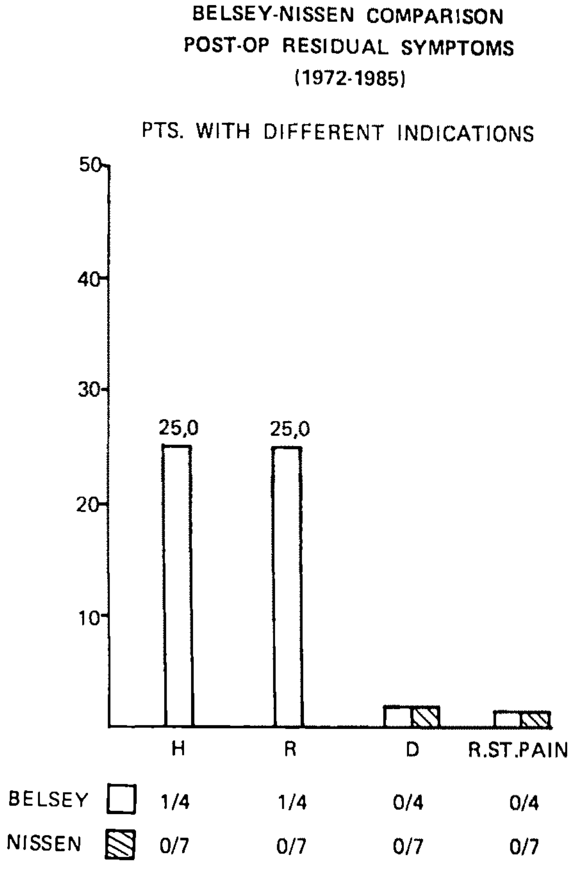

FIG. 4. Postoperative presence of esophageal symptoms in patients, with indications different than proved reflux, submitted to Belsey or Nissen procedures from 1972 to 1985.

TABLE 9. *Gastroesophageal Reflux Belsey–Nissen Comparison (1972–1985); Postop. G.I. Symptoms; Pts. with Different Indications*

Symptoms	Belsey 3/4 (75%)	Nissen 5/7 (71.4%)
Postprandial fullness/early satiety	1/4 (25%)	4/7 (57%)
Nausea/vomiting	—	2/7 (28.6%)
Epigastric pain/pyrosis	1/4 (25%)	—
Inability to belch/vomit	1/4 (25%)	—

and depended on the surgical approach adopted. Minor pulmonary complications developed in 10.8% of patients who underwent thoracotomy; spleen injuries were observed in 5% of patients who underwent laparotomy.

Because these complications were preventable, vigorous attention should be given to pulmonary toilet in the postoperative period for patients selected for a Belsey procedure. When a Nissen fundoplication is planned, it has been suggested that spleen injuries can be minimized by not taking the gastric vessels as part of the operation,[16] and carefully freeing adhesions between the spleen and the diaphragm, if they are present as a consequence of previous abdominal surgery.[10]

Some reports have suggested that the Nissen fundoplication is superior to the Belsey MKIV procedure for the control of gastroesophageal reflux.[1,3,17–19] To this purpose it must be stressed that results of different treatments can be compared only in similarly selected patients. In both series of our study a minority of patients underwent the operation with an indication different than an objectively proved reflux. All of them had satisfactory results in terms of clinical outcome and disappearance of GER symptoms. Most of these patients belong to our initial experience, when less-effective drugs were available and indications for surgery were more liberal.

On the basis of a critical review and strictly following the criteria of proving reflux disease in all subjects who are possible candidates for antireflux surgery, these patients would not be operated on today and would be followed with medical therapy. Therefore to eliminate the possibility that these borderline patients could skew the overall results, they were reported separately. By following these principles, our study shows that the Nissen and the Belsey procedures are equally able to provide a long-term control of reflux in comparable groups of patients.

However the postsurgical presentation of symptomatic patients was different after the Belsey or the Nissen procedure. Esophageal symptoms that develop, even occasionally, after the Belsey procedure, are more frequently due to reflux problems and heartburn is the major complaint. Patients who undergo the Nissen procedure are more prone to present obstructive rather than reflux symptoms, dysphagia presenting the most prominent symptoms.

This tendency is further supported by the patterns of failure we observed in our series: functional symptoms of reflux were present in all patients with failed Belsey; delayed gastric emptying, obesity, and aspeciphic motor abnormalities of the body of the esophagus were identified in all patients with unsatisfactory results. In our overall experience of 64 Belsey MKIV, the incidence of failures is 4.2% in patients with normal motor activity of the body of the esophagus and 33% in those with altered motility. We could not confirm this finding in this selected group of patients because of the exclusions of subjects with reoperations, stenoses, and scleroderma, in which motor abnormalities of the esophageal body are more prominent.

Anatomical failures of the fundoplication due to tightness or slipping of the wrap accounted for most of the unsuccessful results that followed the Nissen procedure.

These data are consistent with other authors' reports, suggesting that the Nissen fundoplication is a more resistant valve than the Belsey repair[17] and dysphagia is the most common cause of reintervention in the majority of patients with failed Nissen.[4] Selection of patients[13] and several technical details have been used to minimize the incidence of postoperative dysphagia[13,12] and the occurrence of postfundoplication symptoms.

Late dyspeptic complaints after antireflux surgery have been frequently described as postfundoplication symptoms.

The terms "gas-bloat syndrome" or "increased abdominal meteorism" have been proposed to define these postfundoplication-related problems; according to different reports, the incidence varies from 10% to 78%.[20–23] We prefer to use the term "postoperative gastrointestinal symptoms."

Indeed the inability to vomit and belch was a consequence of the performed surgery in few patients; nausea, vomiting, and abdominal pain were due to associated gastric or duodenal diseases in others; in the majority of patients the cause of late gastrointestinal symptoms was undiagnosed. Tight fundoplication wrap leading to supercompetence of the cardia,[24] increased aerophagia,[13] and surgical damage of the vagus nerves resulting in functional disorders of the upper intestinal tract[25,26] have been advocated to explain the appearance of these symptoms. In our study these symptoms were not assessed before op-

TABLE 10. *Gastroesophageal Reflux Belsey–Nissen Comparison (1972–1985); Patients with Different Indication; Patient Opinion*

	Belsey (4 Pts.)	Nissen (7 Pts.)
Cured	2 (50%)	4 (57%)
Improved	2 (50%)	3 (43%)
Unimproved/worsened	—	—
Unknown	—	—

erations and, therefore, we cannot determine if they were the result of surgery. In our own experience patients with reflux who did not undergo previous esophageal or gastric surgery complain of postprandial fullness, early satiety, nausea, and vomiting with an incidence as high as 60%.

It is reasonable to assume that before the operation, a sizable group of patients of the present series suffered from these gastrointestinal symptoms, which persisted after operation. These secondary symptoms were not dependent on the type of repair employed, as they were occasional and not disturbing in all patients but those with failed operations. For these reasons they did not restrict the overall acceptance of this surgery.

In conclusion our study shows that the approach adopted for the antireflux surgery affects the rate and type of postoperative morbidity: the Belsey MKIV procedure has a slightly greater incidence of complications due to pulmonary problems; visceral injuries are more frequently observed after the Nissen fundoplication.

In addition the Belsey repair carries a significant incidence of incisional pain, which is not observed after the Nissen procedure. Nevertheless, 85% to 90% of long-term control of reflux symptoms is equally achievable after either procedure in comparable groups of patients. After the Belsey or Nissen procedure, differences might be expected regarding patterns of failures and residual esophageal symptoms: early appearance of severe obstructing symptoms requiring reoperation is more frequently observed after Nissen fundoplication. Obstruction is rarely a complication of the Belsey procedure and recurrence of reflux symptoms is the most common cause of unsuccessful long-term results. Late gastrointestinal symptoms vary and are equally similar and frequent after either procedure; however they are rarely disturbing and do not affect the overall 80% to 85% rate of patient acceptance of the antireflux surgery performed.

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Misoprostol *Versus* Antacid Titration for Preventing Stress Ulcers in Postoperative Surgical ICU Patients

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Bleeding from gastroduodenal lesions is a potentially life-threatening complication in patients subjected to overwhelming physiologic stress. Titration of gastric contents with antacid was the first prophylactic treatment regimen proved to decrease the incidence of bleeding and remains the standard by which other methods are compared. We designed a prospective double-blind, double-placebo study comparing the effectiveness of antacid titration with fixed doses of a synthetic prostaglandin E_1 analog (misoprostol) for preventing stress gastritis and bleeding. To assess the success of each treatment regimen, we did endoscopic examinations before operation, 72 hours after operation, and after the patient had completed the study. A total of 281 patients entered the study (140 misoprostol, 141 antacid). The two groups were comparable with respect to preoperative parameters and type of operation. We found no statistically significant differences between the two treatment groups concerning upper gastrointestinal tract lesions or serious adverse effects. No clinically evident upper gastrointestinal hemorrhage occurred in either group. Mean gastric pH, measured at two-hour intervals during the initial 72 hours, was maintained at 4.0 or higher in both groups. We conclude that fixed-dose misoprostol is as effective as intensive antacid titration in preventing stress ulcers and bleeding in surgical ICU patients.

NEARLY ALL UNTREATED patients in intensive care units develop either endoscopically proved gastroduodenitis or stress ulcers unless prophylaxis is instituted.[1-3] Without preventive treatment, stress bleeding will occur in 6% to 25% of patients, and in this group the mortality rate approached 80%.[2] Respiratory failure, sepsis, trauma, heart failure, peritonitis, and renal failure are associated with higher rates of stress ulcers and bleeding.[2,4,5] Currently the most effective prophylaxis is hourly titration of gastric pH to approximately 4.0 with antacid.[6] While antacid treatment has proved efficacy, it is very labor intensive.

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An alternative to antacids are H-2 blockers; the best studied is cimetidine. However cimetidine may not be as effective as antacids for preventing stress-induced lesions and bleeding. Some reports claim that they are equally effective,[6] while others suggest that fixed-dose cimetidine does not consistently maintain gastric pH higher than 3.5.[7] Failure of cimetidine to control acidity in stressed surgical ICU patients ranges from 15% to 35% and is associated with upper gastrointestinal bleeding, especially in patients with high stress-severity indexes and sepsis.[7,8]

A new alternative to cimetidine and antacids is misoprostol, a prostaglandin E_1 analog that has cytoprotective properties and diminishes gastric acid secretion. It is thus potentially useful for preventing stress ulcers.[2,9] In animals it has been shown to protect the gastric mucosa against salicylate injury and ulcer formation.[10] In man misoprostol inhibits basal and stimulated gastric acid secretion and protects the gastric and duodenal mucosa against a variety of injurious substances.[11] We designed this study to compare the efficacy of misoprostol with antacid titration of gastric pH for preventing stress ulcers and bleeding in postoperative surgical ICU patients.

Materials and Methods

Fifteen physician-investigators at 16 university-associated medical centers enrolled 371 patients scheduled to undergo major surgical procedures. The patients were expected to require at least 48 hours of postoperative monitoring in an ICU. Subjects with additional risk factors

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such as sepsis, trauma, electrolyte imbalance, diabetes, major burns, respiratory failure requiring ventilator assistance, congestive heart failure, arrhythmias requiring medication, or a need for steroids were included. Major exclusion criteria were active peptic ulcer disease, esophageal, gastric, or duodenal malignancies, esophageal varices, gastric outlet obstruction, acute renal failure, concurrent therapy with salicylates, nonsteroidal anti-inflammatory drugs, anti-ulcer therapy, or anti-neoplastic agents. The Institutional Review Board at each of the study sites approved the protocol. Each patient gave written informed consent.

Before randomization each patient underwent an endoscopic examination of the upper gastrointestinal tract to exclude pre-existing lesions. The appearance of the gastric and duodenal mucosa was rated according to a standard grading scale (Table 1). Endoscopic examinations were repeated after 72 hours of drug administration and at completion of the study.

Acceptable candidates were randomly assigned to each group and they received either tablets containing 200 mcg of misoprostol (Searle Inc., Skokie, IL) every four hours plus placebo liquid antacid every two hours, or placebo tablets every four hours plus magnesium-aluminum hydroxide liquid antacid (Maalox TC, Rohrer Pharmaceuticals, Fort Washington, PA) every two hours.

Tablets were dissolved in 20 mL of water and administered six times daily through a nasogastric tube, or were given orally if no tube was in place. Antacid or placebo liquid was administered every two hours at a dose of 10, 20, 40, or 80 mL, increasing the dose upward as necessary during the first 72 hours to maintain gastric pH at 4.0 or higher. Samples were aspirated through the nasogastric tube every two hours and gastric pH was measured using litmus paper. After 72 hours repeat endoscopic examinations were done and the liquid antacid or placebo was titrated downward to 20 mL every four hours. Study patients were treated for a maximum of 14 days or until they were able to take 1500 calories orally for at least one day. All patients entered into the protocol were evaluated for safety. Patients who met the following four criteria were evaluated for outcome: (1) completed at least three days in the study; (2) took at least 80% of the assigned medication; (3) did not withdraw from the study except for side effects of the medication; (4) had sufficient follow-up endoscopy information to permit outcome evaluation.

TABLE 1. *Endoscopic Evaluation of Gastroduodenal Mucosa*

Grade	Description
0	Normal Mucosa
1	Slight diffuse mucosal hyperemic changes
2	A single hemorrhagic lesion or one area of marked patchy erythema
3	2–5 hemorrhagic lesions
4	6–10 hemorrhagic lesions partially confluent or connected with areas of patchy erythema
5	Large area of confluent hemorrhagic lesions
6	Erosions with white bases surrounded by erythematous edges
7	Well-defined ulcer craters

Therapeutic success required absence of clinically evident upper gastrointestinal bleeding and satisfactory prevention of endoscopically proved gastrointestinal lesions during the treatment period. We defined clinically significant bleeding as hematemesis, melena, hematochezia, or red blood through the nasogastric tube that did not immediately clear after a 500-mL normal saline lavage; or a drop in hemoglobin of 2 g/% or more for which other causes of bleeding had been ruled out. The cause of any significant postoperative bleeding was investigated endoscopically.

Endoscopic scores were used in two ways to evaluate therapeutic success. In the first case, we used a strict criterion and defined successful prophylaxis as no increase from the initial preoperative endoscopic score. In the second case, we used a looser criterion and considered prophylaxis successful if the gastric or duodenal lesion score did not increase to 5 or more (erosions or ulcer craters).

Statistical Analysis

The results from all 16 study sites were pooled. The principal objective was to compare the efficacy of misoprostol and antacid in preventing peptic stress bleeding and ulcers in surgical ICU patients. Because this was a multicenter trial, the analysis tested for consistency of results among investigators using log-linear analysis with a model that included investigator, treatment group, outcome, and interactions factors. To assess whether the randomization was successful, the two treatment groups were compared with respect to sex, race, and age using the Pearson chi square test. Outcome assessment was based on gastrointestinal lesion scores or upper gastrointestinal bleeding and required that the patient complete the study. The ratio of patients satisfying the four criteria described above for successful prophylaxis were compared for both groups. In addition the ratio of patients in each group with initial endoscopic scores of 0 or 1 and follow-up scores of less than 2 (lesion prevention) or less than 5 (prevention of clinically significant lesions) was compared. These comparisons were made using Pearson's chi square test or Fisher's exact test. The distribution of initial lesion scores in both treatment groups was tested using a Wilcoxon two-sample test. The proportions of patients in the two treatment groups experiencing diarrhea were compared using log-linear analysis. Differences between the two groups with respect to laboratory values were compared using analysis of variance. The protocol was designed to require a minimum of 270 fully evaluable patients to complete the study (135 in each group). This sample size is sufficient to detect differences of 20% or more between two treatment groups (p = 0.05; power = 0.90) with two-sided tests of significance. That is, this study size should detect a clinically significant difference between misoprostol and antacid that is greater than 20%.

Results

A total of 371 subjects were enrolled; 187 patients received misoprostol and 184 received antacids titrated to maintain gastric pH at or above 4.0. The study population included the following operative categories: trauma 72 (19.4%); emergency general surgery 95 (26.6%); elective general surgery 93 (25.1%); elective cardiothoracic surgery 10 (2.6%); elective vascular surgery 87 (23.5%); and renal transplant 14 (3.8%).

There were no statistical differences between the two treatment groups with respect to age, sex, or race (Table 2). They were also comparable in mean height, weight, and vital signs on admission, and these did not differ with respect to study site. Initial gastric lesion scores were 0 or 1 in 88% of the patients, and initial duodenal lesion scores were 0 or 1 in 96% of the patients, with no significant differences between the two treatment groups (p = 0.141 and 0.848, respectively).

All 371 patients were evaluated for safety of the prophylaxis regimen. Of these, 141 receiving misoprostol and 140 receiving antacid met the four criteria for evaluation of primary outcome.

TABLE 2. *Characteristics of Study Population*

Treatment Group	Misoprostol	Antacid	p value
Total number with complete information	187	181	
Age (years)			0.686*
<30	25	24	
30–39	13	17	
40–49	19	19	
50–59	38	46	
60–69	60	51	
>70	32	24	
Sex			0.638†
Male	152	153	
Female	35	24	
Race			0.146‡
Caucasian	100	99	
Negro	62	72	
Hispanic	18	8	
Other	7	4	

* Wilcoxon Rank-Sum.
† Chi square, 1 d.f.
‡ Chi square, 3 d.f.

TABLE 3. *Patients with Follow-up Endoscopic Scores Less than 2*

Treatment Group	Misoprostol*	Antacid*	p value†
72-hour gastric Endoscopy	56/147 (38.1%)	53/142 (37.3%)	0.892
72-hour duodenal Endoscopy	143/156 (91.7%)	150/159 (94.3%)	0.352
Final gastric Endoscopy	61/120 (50.8%)	63/123 (51.2%)	0.952
Final duodenal Endoscopy	117/124 (94.4%)	126/136 (92.6%)	0.578

* All enrolled patients with initial endoscopic scores of 0 or 1.
† Chi square comparison.

Evaluation of Efficacy

The proportion of patients satisfying the strict criteria of therapeutic success (no change in lesion score) was slightly higher in the antacid group (31.4% antacid *vs.* 26.2% misoprostol), but the difference was not statistically significant (p = 0.337). Using the looser criteria (mucosal scores remaining less than 5), the overall success rates were also similar (69.2% antacid *vs.* 70.5% misoprostol; p = 0.820). No clinically evident bleeding occurred among the patients of either treatment group. Comparable numbers of patients completed the 14 days of treatment or were released earlier, having met the dietary requirement. By the eighth day, only 16% of the misoprostol group and 21% of the antacid group remained in the ICU (p = ns). Total time of nasogastric medication administration was also somewhat shorter in the misoprostol group (655 patient days *vs.* 731 patient days in the antacid group), but again these differences were not statistically significant.

Follow-up lesion scores were compared for all patients enrolled in the two groups with initial endoscopic scores of 0 or 1 and follow-up scores of less than 2. Results for the 72-hour and final gastric follow-ups and for the 72-hour and final duodenal follow-ups were comparable between treatments, with no statistically significant differences (Table 3). When follow-up lesion scores of less than 5 were counted as successful prevention of clinically significant lesions (Table 4), the numbers and proportions of successes were greater in both treatment groups, but there were no statistically significant differences between groups. We repeated these analyses, stratifying by the number of risk factors present (all patients, 2 or more factors, 3 or more factors) to determine if there were subgroups in whom one of the treatments may have been more effective but we found no significant differences between the treatment groups.

Analysis of pH

The initial pH measurements were similar in the two groups. On the first postoperative day, pH was higher in

TABLE 4. *Patients with Follow-up Endoscopic Scores Less than 5*

Treatment Group	Misoprostol*	Antacid*	p value†
72-hour gastric Endoscopy	121/147 (82.3%)	115/142 (81.0%)	0.771
72-hour duodenal Endoscopy	153/156 (98.1%)	158/159 (99.4%)	0.305
Final gastric Endoscopy	108/120 (90.0%)	108/123 (87.8%)	0.586
Final duodenal Endoscopy	120/124 (96.8%)	134/136 (98.5%)	0.346

* All enrolled patients with initial endoscopic scores of 0 or 1.
† Chi-square comparison.

both groups, probably reflecting the stress and trauma of anesthesia and operations on acid secretion. Thereafter pH levels fell in both groups, but remained consistently higher in the antacid group. Mean pH levels in the misoprostol group were always at or above 4.0 (Fig. 1), reflecting the antisecretory properties of misoprostol in doses greater than 100 μg.[12] In both groups there were statistically significant inverse correlations between follow-up lesion scores and average pH levels in individual patients.

Safety

Fifteen patients in the misoprostol group and 13 in the antacid group died during the study or shortly thereafter due to underlying disease states or surgical complications. All deaths and serious complications were reviewed by the Institutional Review Boards of each respective medical center and none of these deaths were attributed to study medications.

The most common adverse event was diarrhea, defined as three or more watery stools within a 24-hour period, representing a clinically significant change from the patient's normal habits. We found this in 25.3% of the misoprostol group and in 22.8% of the antacid group, an insignificant difference ($p = 0.58$). This difference was similar to those found in other studies.[13] Statistically significant differences between the two groups were observed in some laboratory tests, namely serum bicarbonate and serum phosphorus levels. An average increase of 1.75 mEq/l in serum bicarbonate concentration occurred in the antacid treated group compared to a decline of 0.23 mEq/L in those treated with misoprostol. While this difference is statistically significant ($p = 0.001$) it is of questionable clinical significance. Of 163 patients treated with antacid, 33 (20%) developed final serum bicarbonate concentration elevated to 30 mEq/L. Among misoprostol recipients only 16 of 175 (9%) had similar elevations ($p = 0.004$).

Phosphorus concentrations fell 0.38 mg/dL in the antacid group, but rose by a similar amount in misoprostol recipients ($p = 0.003$). Of 132 patients treated with antacid, 32 (24%) developed final inorganic phosphorus concentrations of less than 2.5 mg/dL. Only 21 of 144 patients

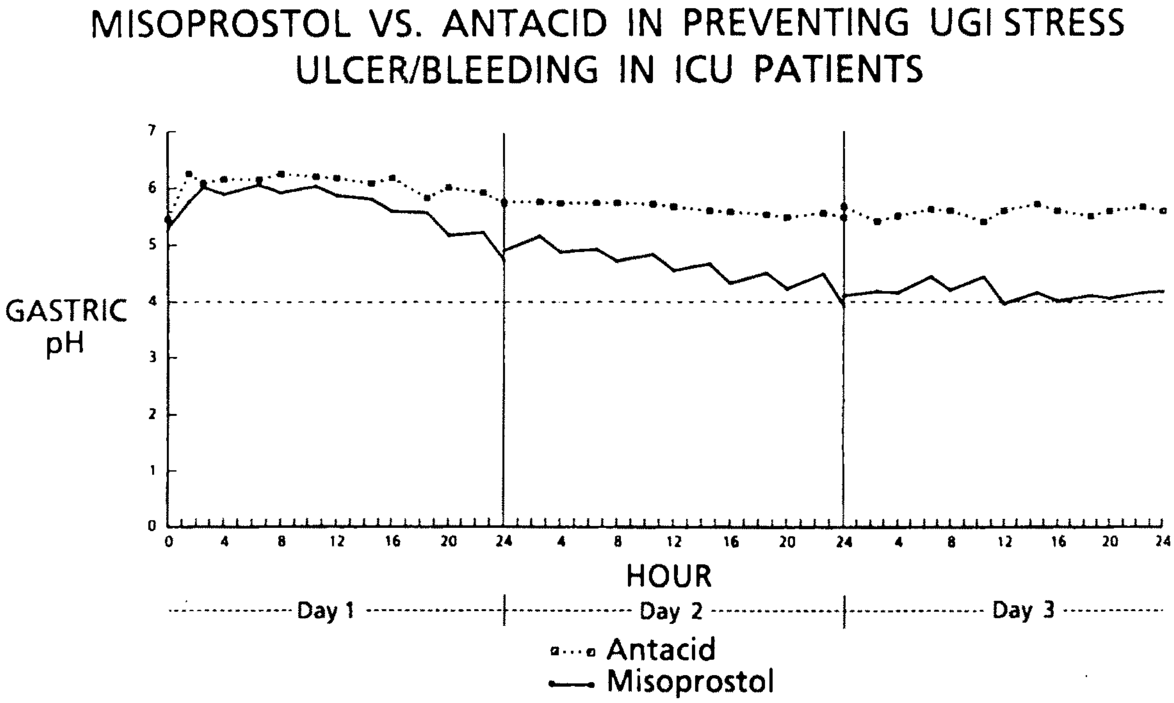

FIG. 1. Graph showing the pooled values for pH at 1-hour intervals. The gastric pH levels fell in both groups but were consistently higher in the antacid group. The average pH in both groups remained greater than 4.0.

(15%) in the misoprostol group had phosphorus levels of less than 2.5 ($p = 0.042$).

Discussion

Because acute gastrointestinal bleeding from stress ulceration can be life-threatening in postoperative ICU patients,[1-3] some form of preventive medication is usually given. Maintaining the gastric pH of 4.0 or greater by titrating with antacids is the most effective prevention of stress ulcer bleeding, although it is time-consuming.[5,8] In their prospective controlled trial of this regimen, Hastings et al.[14] reduced bleeding rates in ICU patients from 25% in a placebo group to 4% in a group receiving antacid.

A fixed-dose drug regimen that does not require pH monitoring and is as effective as antacid titration, would be an important advance in ICU care, allowing more efficient use of nursing staff. Initially H-2 blockers seemed promising. However several studies have shown that cimetidine is not as effective as antacid in preventing stress-induced bleeding and is most likely to fail in patients with multiple risk factors or sepsis.[7,8] The association between successful prophylaxis of stress bleeding by antacid and the maintenance of pH level at 4.0 or greater has been described repeatedly in the literature. In Hastings' study,[14] gastric pH in the antacid group stayed between 7.0 and 8.0, but in untreated controls it varied widely (from 1.0 to 8.0). Zinner et al.[8] found that antacids consistently kept the pH at 4.0 or greater, cimetidine was less reliable than antacids, and untreated patients had a mean pH value of 3.0. In a placebo-controlled trial of cimetidine for preventing upper gastrointestinal bleeding in medical ICU ventilator-dependent patients, mean pH during cimetidine treatment was 4.8, compared to 3.1 in patients give a placebo.[15] An explanation of the disparate results of studies of H-2 blockers is suggested by Martin et al.[7] and may reflect the incidence of sepsis in the various study populations. They found that cimetidine was most likely to fail to maintain gastric pH greater than 4.0 in patients with sepsis as a risk factor. However stratifying the groups with respect to the number of risk factors did not produce data supporting the use of either treatment in our study.

Mean pH levels were consistently higher in the antacid group, an expected result of periodic antacid titration. In the misoprostol group, the mean pH level was consistently greater than 4.0. This pH level can probably be attributed to the acid antisecretory effect of misoprostol in doses greater than 100 μg as were given in this study.[12,16]

A unique feature of this study was routine postoperative evaluation of the upper gastrointestinal tract by endoscopy. Previous prospective trials used bleeding as the dependent variable. However we did not believe that this variable was sensitive enough to determine the condition of the mucosa. We wanted to learn whether effective treatment prevents stress ulcers as well as decreases the rate of upper gastrointestinal tract bleeding. We found that misoprostol and antacid were equally effective in preventing upper gastrointestinal lesions, success being defined as no increase in gastric or duodenal lesion scores at 72 hours. Misoprostol had a success rate of 39.4% and the antacid success rate was 39.3% ($p = 0.991$), that is, approximately 60% of patients developed some increase in gastric lesion score, and the increases were equal in the two groups.

With respect to side effects, the two medications were similar. Both misoprostol and antacids have been reported to produce diarrhea. In this study both treatment groups experienced a similar incidence of diarrhea (misoprostol, 23%; antacid, 25%) in rates similar to previous trials.[13] There were statistically significant differences in some laboratory studies between the two groups that we believe were probably not clinically significant. Patients receiving antacids developed a significant increase in serum CO_2, while patients receiving misoprostol did not. The slight difference in serum CO_2 levels is probably not clinically significant, although in individual patients hypercarbia associated with metabolic alkalosis can impair the weaning of patients from ventilators. The decrease in serum phosphate levels seen in the antacid group could be due to binding of phosphate to antacid in the gastrointestinal tract.

Essentially we could find no important differences with respect to safety and efficacy between fixed-dose misoprostol and antacid titration of gastric acidity with a magnesium aluminum hydroxide antacid in a randomized group of 281 patients. Thus the appropriate choice of a drug for stress ulcer prophylaxis must rest on other factors such as price and convenience. To date no price has been determined for misoprostol. However it is probably fair to say that it will be more expensive than antacids. If fixed-dose misoprostol is to be compared with antacids for stress ulcer prophylaxis, the additional time and equipment required for nurses to titrate gastric acid to levels greater than 4.0 with antacids should also be considered. We expect that this cost is considerable.

We conclude that fixed-dose misoprostol and antacid titration are similarly effective in preventing clinically evident upper gastrointestinal tract hemorrhage and the development of endoscopically proved stress lesions. Although at this time the cost of treatment with misoprostol is not known, it will probably be more expensive than antacids. However misoprostol has advantages over antacid titration in ease of administration and should significantly reduce the amount of nursing time required for stress ulcer prophylaxis.

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Lymph Node Metastases of Gastric Cancer

General Pattern in 1931 Patients

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The incidence of metastases from gastric adenocarcinoma to various regional lymph node stations was studied after meticulous node dissection and correlated to survival in 1931 resected patients. The incidence of metastases increased with deeper tumor invasion into the stomach wall. Deposits were most common in some perigastric node stations, and their distribution was clearly related to the location of the tumor. Some nonperigastric node stations also were frequently involved, *e.g.*, those around the left gastric artery or in the splenic hilum, and may be considered primary draining nodes. Skip metastases to distant nodes were found in a few per cent of perigastric node-negative patients. Deposits in nodes around the middle colic artery, but not in any other upper abdominal node stations, were incompatible with 5-year survival rates. The analysis favors a so-called R2 or more extensive resection for cancers invading beyond the submucosa.

THE RESULTS OF OPERATIONS for advanced stomach cancer, in contrast to the so-called early gastric cancer (EGC), are generally reported to be discouraging, with little if any improvement attributable to the surgical technique during the last decade.

An analysis of more than 5000 resections for gastric cancer at our hospital showed, however, continuing improvements of survival rates within each tumor node metastasis (TNM) stage for every 5-year period since 1962. The changes were most impressive in stages II and III, in which the 5-year survival rates increased from 57% to 83% and from 33% to 50%, respectively. This is not explained by the simultaneous decrease in operative mortality from 3% to 0.6%, but possibly may be related to a more aggressive surgical approach in curatively aimed resections with more consistent use of systematic lymph node dissection, and more frequent total gastrectomies and resections of involved neighboring organs.

The relative importance of the lymph node dissection is difficult to assess because few randomized controlled studies exist.[1] Such studies are considered inappropriate in Japan, where there is wide consensus on the desirability of a standardized extensive node dissection as proposed by the Japanese Research Society for Gastric Cancer.[2]

Proponents of thorough node dissection argue that many long-term survivors after resection of stomach cancer had node metastases,[3-5] that the procedure gave better survival rates than in historic controls,[6,7] and decreased the incidence of local recurrence[8,9] without added morbidity or mortality.[8,10,11]

On the other hand, higher operative morbidity[1] and mortality rates, as well as lower 5-year survival rates after aggressive surgery have been claimed,[12] and the possibility to prevent the local recurrences found at second-look operations by extended initial resection has been questioned.[13]

The evaluation of systematic node dissection by nonrandomized studies is complicated by the fact that the procedure also may change the staging by detection of micrometastases that speculatively may have little impact on the survival, as in breast cancer.[14] In this way patients with a relatively poor prognosis, in a low stage according to conventional node dissection, may move to a higher stage in which their prognosis is better than average. This stage migration phenomenon could lead to improved prognosis in both stages even if the node dissection had no therapeutic effect.

We have analyzed lymph node metastases and survival rates in 1931 meticulously dissected consecutive patients

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with resected advanced gastric cancer to see whether the findings could guide the node dissections in gastric cancer.

Patients and Methods

Patients

Primary advanced (non-EGC) carcinomas of the stomach were resected in 1931 consecutive patients at the National Cancer Center Hospital in Tokyo between 1972 and 1986. Their average age was 59 years, with a male: female ratio of 2:1.

Operative Procedures

Distal subtotal gastrectomy was performed in 57%, total gastrectomy in 38%, and proximal subtotal gastrectomy in 5% of the cases. A margin of 2 cm was required for circumscribed tumors, and of 5 cm for less-well-defined tumors. Neighboring organs were resected in 41% of the operations, most frequently the spleen (24%) and pancreas tail (13%).

The lymph node stations 1 to 16 according to the Japanese classification[2] (Table 1) were palpated and, if needed, evaluated by frozen section during operation. The perigastric nodes, excluding the left cardial nodes (number 2) in distal gastrectomy, were removed *en bloc* with the stomach while other stations were removed separately or in groups to achieve at least a so-called R2 resection[2] (Table 2) in 78% of all resections. This removes perigastric nodes as described, nodes around the common hepatic artery (CHA), the left gastric artery (LGA), and celiac artery (CA), and for proximal cancers also the nodes in the splenic hilum, along the splenic artery (SA), and the left cardial nodes. In the case of metastases, the aim of the dissection was to have a margin of one uninvolved group of lymph nodes distal to the most peripheral involved group of node stations.

TABLE 1. *Numbering of Upper Abdominal Lymph Node Stations*

Station Number	Location
1/2	Right/left side of cardia
3/4	Along lesser/greater curvature
5	Suprapyloric, along RGA
6	Infrapyloric
7	Along LGA
8	Along CHA
9	Around CA
10	At the splenic hilus
11	Along SA
12	In the hepatoduodenal ligament
13	Behind the pancreas head
14	At the root of the mesentery (SMA)
15	Along MCA
16	Paraaortic

CA, celiac artery; CHA, common hepatic artery; LGA, left gastric artery; MCA, middle colic artery; RGA, right gastric artery; SA, splenic, artery; SMA, superior mesenteric artery; Station numbers 1 to 6 are perigastric.

TABLE 2. *Groups of Node Stations Used to Define the Extent of Node Dissection*

	Location of the Tumor			
Station Number	A, AM	M, MA, MC	C, CM	AMC, MAC, MCA, CMA
1	N2	N1 —	—	—
2	N3	N2	N1 —	—
3, 4	N1 —	—	—	—
5, 6	N1 —	—	N2	N1
7–9	N2 —	—	—	—
10, 11	N3	N2 —	—	—
12–14	N3 —	—	—	—
15, 16	N4 —	—	—	—

N1, group of node station closest to the tumor; N2–N3, more distant groups.

CA, celiac artery; CHA, common hepatic artery; LGA, left gastric artery; MCA, middle colic artery; RGA, right gastric artery; SA, splenic, artery; SMA, superior mesenteric artery; Station numbers 1 to 6 are perigastric.

Macroscopic Evaluation

The tumor was classified according to Borrmann[15] as type 1, nonulcerated polypoid; type 2, ulcerated elevated with well-defined border; type 3, ulcerated with partially diffuse infiltrating border; and type 4, diffusely invading tumor. Its size and location were registered, with the upper, middle, and distal thirds of the stomach (C, M, and A, respectively) defined by two lines dividing each curvature into three equal parts. The position on the circumference was related to the curvatures and anterior/posterior walls. The areas of tumor growth were recorded in order of importance, *e.g.*, M, MA, MAC, MCA, and correspondingly for the circumferential position.

Histologic Evaluation

The cancers were classified[16] as papillary, tubular well or moderately differentiated, poorly differentiated, signet ring cell type, mucinous, and rare adenosquamous tumors. Squamous cell carcinomas, carcinoids, and nonepithelial tumors were excluded. The depth of invasion into the stomach wall and metastases to lymph nodes dissected from the fresh specimen, on an average more than 30 nodes, were recorded.

Analysis

Computer-based files contained the above information and results of follow-up, including postoperative course, time, and main site of recurrence, and time and cause of death. Cumulative 5-year survival rates, including operative mortality, were calculated for subsets of patients defined by combinations of the registered variables, with 5% standard error calculated according to Greenwood.[17] Pa-

TABLE 3. *Location, Depth of Invasion, and Macroscopic Type of 1931 Resected Gastric Cancers*

Main area of tumor	
Upper third	25%
Middle third	38%
Distal third	37%
Depth of invasion	
Muscularis	17%
Subserosa	13%
Serosa	47%
Neighboring organs	24%
Borrmann's type of tumor	
1	4%
2	28%
3	53%
4	13%
Unclassifiable	2%

tients in whom a node station subject to analysis had not been dissected were excluded from the calculations.

Results

Spectrum of Tumors

The locations, depths of invasion, and macroscopic types of the tumors are detailed in Table 3. C tumors were most frequently located at the lesser curvature (43%) and posterior wall (35%), with these positions in 44% and 21%, respectively, of M cancers. For A tumors, the lesser and greater curvatures accounted for 33% and 20%, the anterior and posterior walls for 17% to 18% each, and 11% were circumferential.

The most common histologic type was poorly differentiated adenocarcinoma (37%). This and the signet ring cell cancers (16%) are the forms most closely corresponding to Lauren's diffuse type.[18] The differentiated papillary and tubular cancers resembling the intestinal tumors comprised 41%, while a few tumors could not be classified by Lauren's criteria.

Overall Pattern of Metastases

Twenty-three per cent had macroscopically and 26% microscopically uninvolved nodes. The incidence of node metastases varied between 9% and 53% in the perigastric station numbers 1 to 6, with relatively high incidences also in station numbers 7 to 9 and 11, *i.e.*, around the CA and its branches (Table 4). Abdominal node metastases were found outside the defined stations in 0.8% of the patients. The depth of invasion correlated strongly with the incidence of metastases. Subdivision according to histologic tumor type showed a slightly higher incidence of metastases and a slightly lower 5-year survival rate for patients with tumors of the diffuse histologic pattern (Table 4). The anatomic distribution of the primary tumors in node-positive patients was very similar to that in node-negative cases.

Tumor Location and Metastatic Pattern

Tumors confined to one of the C, M, or A thirds of the stomach were analyzed with subdivision according to the position of the tumor on the circumference. The incidence

TABLE 4. *Incidence of Metastases to Individual Node Stations in Subsets of 1931 Cases of Gastric Cancer*

Node Station Number	Incidence % (5-Year Survival Rate, %)					
		Histopathology		Depth of Invasion		
	All Cases	Diffuse	Intestinal	PM*	S1	S3
	(43%)	(40%)	(48%)	(82%)	(50%)	(15%)
1	25 (19%)	27	22	5	17	37
2	10 (9%)	11	8	2	15	21
3	53 (29%)	56	48	25	48	63
4	39 (22%)	42	33	16	39	55
5	9 (17%)	9	9	2	5	15
6	34 (23%)	35	31	17	28	47
7	35 (19%)	38	31	9	29	52
8	25 (16%)	26	23	7	23	41
9	20 (16%)	22	18	5	14	33
10	9 (12%)	11	6	1	3	20
11	12 (6%)	14	9	2	7	28
12	8 (9%)	8	7	2	5	15
13	2 (2%)	2	3	0	1	6
14	4 (6%)	4	3	0	1	10
15	1 (0%)	1	1	0	0	2
16	8 (2%)	9	6	0	4	17
Other abdominal nodes	1	1	1	0	0	2

* PM, muscularis propria; S1, suspected serosal invasion; S3, invasion to contiguous structures.

TABLE 5. *Incidence (Percentage) of Node Metastases from Cancers in Various Parts of the Stomach*

Lymph Node Station Number	Location of the Tumor (A, M, C)						
				A tumors on the			
	A n = 339	M n = 318	C n = 150	Lesser Curvature	Anterior Wall	Greater Curvature	Posterior Wall
1	7	16	31	11	0	3	7
2	0	1	13	(0–1)	(0–1)	(0–1)	(0–1)
3	38	40	39	42	27	32	33
4	35	31	11	25	44	49	26
5	12	3	2	15	3	7	0
6	49	15	3	39	32	62	30
7	23	22	19	25	21	23	11
8	25	11	7	34	9	25	15
9	13	8	13	16	3	12	7
10	0	2	10	(0–1)	(0–1)	(0–1)	(0–1)
11	4	4	12	7	0	1	0
12	8	2	1	12	3	6	0
13, 14, 15, 16	(0–5)	(0–5)	(0–5)	(0–5)	(0–5)	(0–5)	(0–5)

A, M, C: distal, middle, and proximal thirds of the stomach, respectively.

of metastases to any perigastric node station was highest when the tumor was located close to it, even though there was little variation in the metastatic pattern along the lesser curvature between tumors in the different thirds. Station numbers 2 (left cardial) and 5 (suprapyloric, RGA) were low-incidence stations for all locations of tumors (Table 5). The position of the tumor on the stomach circumference had a similar impact, as shown for A cancers (Table 5). Similarly C tumors along the lesser curvature or on the anterior or posterior walls had splenic hilar node metastases in up to 6%, compared to 32% for tumors at the greater curvature (not shown).

Perigastric Nodes and Skip Metastases

Eleven per cent of the patients (215 cases) had histologically uninvolved perigastric nodes if confirmation was required also for station number 2, which often was not dissected in distal cancers. Of these patients, 2% to 4% had metastases to each of station numbers 7 to 11 and 1% to each of station numbers 12 (PHA) and 16 (paraaortic).

Of all patients, including those in whom station number 2 had not been dissected, 519 did not have deposits in the perigastric stations studied. They had the same incidences of nonperigastric node deposits as given above. The most frequent locations for nonperigastric node metastases in the absence of perigastric deposits were station numbers 7 (LGA) and 8 (CHA), each in 4% of the patients, with 5-year survival rates of 35% and 49%. Both stations were affected in one third of these patients. Station number 9 (CA) was diseased in 12 of 519 patients (2%), five of whom also had involvement of station number 8. Station number 12 (PHA) had deposits in seven cases, a few of whom were positive also in station numbers 7 and 8. More distant metastases occurred in only two patients who had metastases to station numbers 9 and 16. Skip metastases to station numbers 8 and/or 12 gave a 5-year survival rate of 49% and 43%, respectively. Other localizations of skip metastases correlated with survival rates of 20% to 35% except along the SA, which was incompatible with 5-year survival.

Patients with node deposits in only one of the six perigastric node stations were separately analyzed (Table 6). All involved stations, except number 5, along the RGA correlated to relatively frequent metastases to the LGA station number 7. All stations except number 2 also had a possibility of spread to station number 8 at the CHA.

TABLE 6. *Other Peripheral Node Deposits in Cases with Only One of the Perigastric Node Stations Involved*

Involved Nodes	Number of Cases (5-Year Survival, %)	Incidence (%) of Deposits in Station Numbers									
		7	8	9	10	11	12	13	14	15	16
1	26 (46)	35	8	12	15	19	0	0	0	0	0
2	7 (38)	14	0	0	0	14	0	0	0	0	0
3	85 (62)	35	8	21	5	9	0	1	0	0	5
4	20 (50)	25	15	15	25	5	0	0	5	0	5
5	7 (100)	0	14	0	14	14	0	0	0	0	0
6	81 (57)	12	26	12	0	0	7	3	4	1	5

Station numbers 10 and 11, at the splenic hilum and along the SA, relatively often were involved when nodes around the cardia or along the proximal part of the greater curvature were diseased. The widest pattern of spread was seen in metastases to the subpyloric station, number 6.

Metastases to Nonperigastric Nodes

The incidences of metastases to each of station numbers 7 to 16 are shown in Table 4. Station numbers 7 to 9 had the highest incidences, followed by numbers 10 to 12 and 16, with lowest incidences in numbers 13 to 15. Some anatomic patterns will be described.

The LGA channel (number 7). Six hundred seventy-six patients had this involvement, with a 5-year survival rate of 19%. Their primary tumors were located in the C third in 23%, M third in 40%, and A third in 36%. Positivity correlated with deposits in station number 3 in 85% of the cases, but also with metastases to station numbers 4 and 6 in more than 50% each. Further spread to station number 9 around the CA occurred in 43% and to the para-aortic nodes (number 16) in 17% of the patients.

The CHA (number 8) and PHA (number 12) channels. Four hundred eighty-one patients were positive in number 8 nodes and 145 in station number 12, with 5-year survival rates of 16% and 9%, respectively. The main tumor locations were C-M-A in 17%, 35%, and 48% for number 8 node-positive cases and 12%, 29%, and 59% for number 12 node-positive patients. Only 21% of the number 8 node-positive cases were also number 12 node positive, while number 12 deposits correlated with number 8 involvement in 70%. Of the perigastric nodes, number 3 involvement showed the strongest correlation with number 8 and/or 12 deposits. Metastases to station numbers 9 and 16 were found in 51% and 19%, respectively, of number 8 positive cases and in 59% and 35% of number 12 positive patients. There was little correlation with positive findings in the retropancreatic node station number 13. In 40 cases without gross metastases to the liver and peritoneal cavity and no invasion into adjacent organs, metastases to station number 12 gave a 5-year survival rate of 25%.

The CA (number 9) channel. Three hundred ninety-one patients had tumor growth at this place, with a 5-year survival rate of 16%. Their tumor locations were 26% C, and 37% for each of M and A. As expected from the anatomy, only 25 patients had metastases to station number 9 without involvement of any of the stations at the LGA (number 7), CHA (number 8), or SA (number 11), and these patients most frequently had secondary involvement in station numbers 3 (72%) or 4 (44%).

The para-aortic nodes (number 16). This is the most distal resectable intra-abdominal station, to which most lymphatic channels from the stomach converge by the CA, SMA, inferior phrenic, and other arteries. One hundred forty-eight patients with a 5-year survival rate of 2% had metastases to this station, which comprises a wide area on both sides of the supra- and infrarenal aorta that functions as a unit, according to intravital dye staining. The distribution of tumor locations was identical to that of the entire patient material. The CA station was involved in 66% and the SMA channel in 22% of these patients.

Other node stations. The retropancreatic nodes (number 13), the stations at the root of the mesentery along the SMA (number 14) and at the middle colic artery (MCA; number 15) were infrequently involved by tumor, which yielded 5-year survival rates between 0% and 6%. For these patients, the tumors were more commonly located in the A third (42% to 58%) than in the total patient group. The only remarkable correlation to perigastric node positivity was that deposits in station number 13, more often than disease in any other nonperigastric station, correlated with positivity in the subpyloric nodes (number 6).

Discussion

The extent of node metastases and the depth of invasion are the two most important prognostic factors in gastric cancer without distant metastases, and they form the basis for the new TNM classification. A multivariate analysis of our 4710 patients resected between 1962 and 1984 showed that each variable had a relative impact of more than 4.0 on the survival, while the location or histologic type of tumor accounted for variations of 1.5 and 1.2, respectively.[19]

Node metastases can be resected with subsequent long-term survival,[3-5] but opinions differ as to the desirable extent of node dissection.[1,6-9,12,13] The pattern of lymphatic spread was reported to be unpredictable from the location of the tumor[20] and evaluation of nodes by palpation was believed to be unreliable.[21] The lack of correlation between tumor location and pattern of spread was probably related to the study of very advanced tumors, however. Our material with many potentially curable cases with limited dissemination showed an orderly spread to the nodes clearly related to the position of the tumor, which occurred with decreasing frequency along identifiable lymphatic chains along the arteries, and converged to a wide area around the upper abdominal aorta as in a previous, more limited study.[22]

Metastases were found in a few per cent of cases without perigastric node metastases, most commonly around the LGA, CHA, SA, and in the splenic hilus. These are not necessarily true skip metastases: it is not surprising that spread occurs along the LGA or short gastric vessels, or along the irregular dorsal gastric artery to the SA. However true skip metastases to more distal nodes undoubtedly existed, as suggested by intravital dye injections with which stained lymph vessels often passed through lymph node stations without staining of individual nodes (Maruyama K, unpublished observations). Their incidence, however, was low.

Our material was large enough to provide information regarding survival rates in the presence of metastases to individual node stations. As expected, limited spread to perigastric nodes correlated to better survival rates than deposits around the CA, for example, the poorest prognosis being associated with metastases in the hepatoduodenal ligament, behind the pancreas head, at the root of the mesentery, and along the aorta (station numbers 12 to 16). However in patients without gross liver or peritoneal metastases and no invasion of adjacent organs, the 5-year survival rates still were a few per cent after dissection of deposits in the hepatoduodenal ligament and/or around the aorta.

We believe that our collected information now is so large that it can guide our node dissections in individual patients. After abdominal exploration with peritoneal washing for cytology and frozen sections from potentially relevant findings, we decide whether a curative resection is feasible. If so, we follow a preoperative plan for node dissection based on a computer print-out of the incidence of node deposits and survival rates in previous patients matched with regard to age, size, location, and histology of the tumor, and the three most likely depths of invasion as estimated from endoscopy and x-ray examinations. If this analysis shows that metastases to one particular node station were uncommon and/or associated with no long-term survival, the station is not dissected in the absence of abnormal palpatory findings. The resulting operative procedures have, in practice, conformed with the Japanese standard R2 resections[2] (Table 2) or have been more extensive, showing the validity of this concept. In the most superficial EGC tumors, the analysis has often led to a less extensive so-called R1 resection.

In advanced cancer, the perigastric nodes should be removed except for the left cardial station in distal cancers. In addition, nodes along the LGA, the CHA, and SA close to the CA, as well as around the CA itself, should be removed because these stations are closely related functionally, and are separated mostly for the purpose of registration. They had a relatively high incidence of metastases and there was a significant proportion of long-term survivors, between 6% and 19%, for patients with metastases dissected from these stations. In proximal cancers, nodes in the splenic hilum and along the distal SA should also be dissected.

This policy may have to be modified in patients who are not so lean and free from arteriosclerotic complications as Japanese patients generally are (and who recently had an operative mortality rate of 0.6% after gastric resection at our unit).

The possible biologic differences between Japanese and Western gastric cancer are difficult to evaluate. As described, the histologic tumor type was not an important prognostic factor and postulated differences in the relative frequency of intestinal and diffuse cancers in different countries ought not to have a heavy impact on the survival rates. However other unidentified factors influencing the prognosis in different regions cannot be ruled out. It is of interest in this context, that a German study[10] demonstrated incidences of node metastases in the various node stations in curatively resected patients that were very similar to those found in our total material, with station number 3 being most frequently involved, in 57% to 53% of the patients. It seems likely that, regardless of possible geographic differences in aggressivity of stomach cancer, those that give lymphogenous metastases follow the same paths of dissemination.

A recent controlled randomized study[1] failed to show any advantage of R2 resections over more limited node dissections with regard to survival, while operative complications were more common after the R2 procedure. The results of this study may produce information more about the practicability of the R2 procedure in Westerners than about the oncologic adequacies of the compared operations, and the study was based on only 43 patients, with a higher mean age in the R2 group and more total gastrectomies in the R1 group. Moreover the number of nodes recovered were not stated and the description of the procedure does not conclusively state that R2 resections in the Japanese sense actually had been performed. Based on our findings and on the negligible operative mortality rate in our patients, we favor the R2, or more extensive, dissections in curatively aimed resections for advanced gastric cancer.

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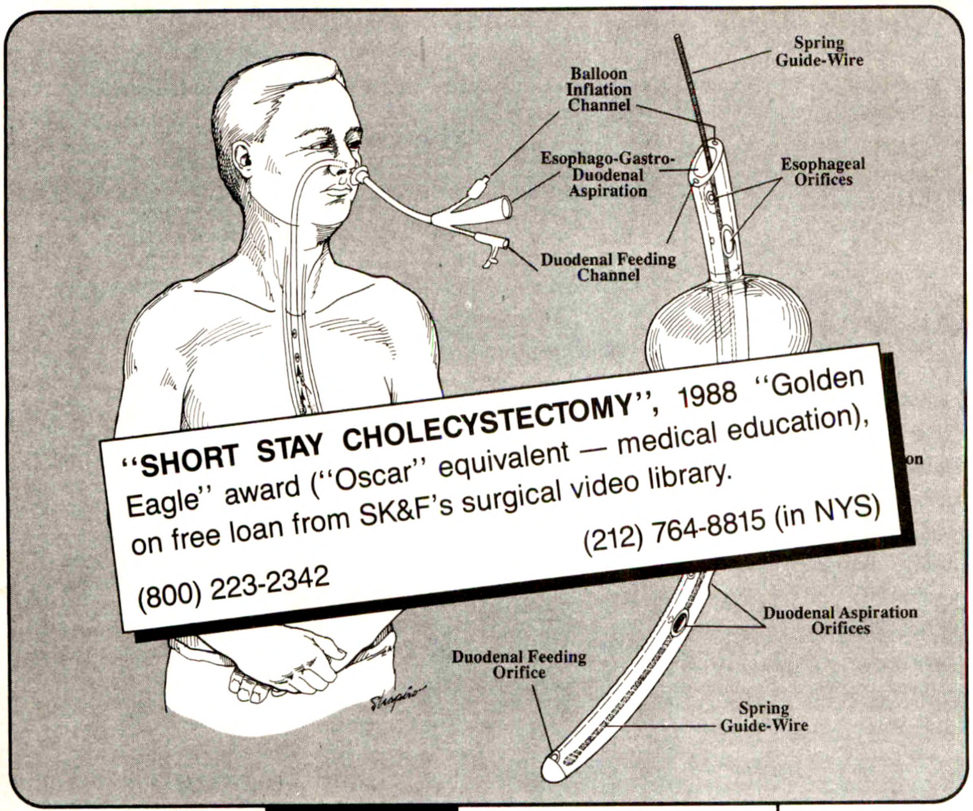

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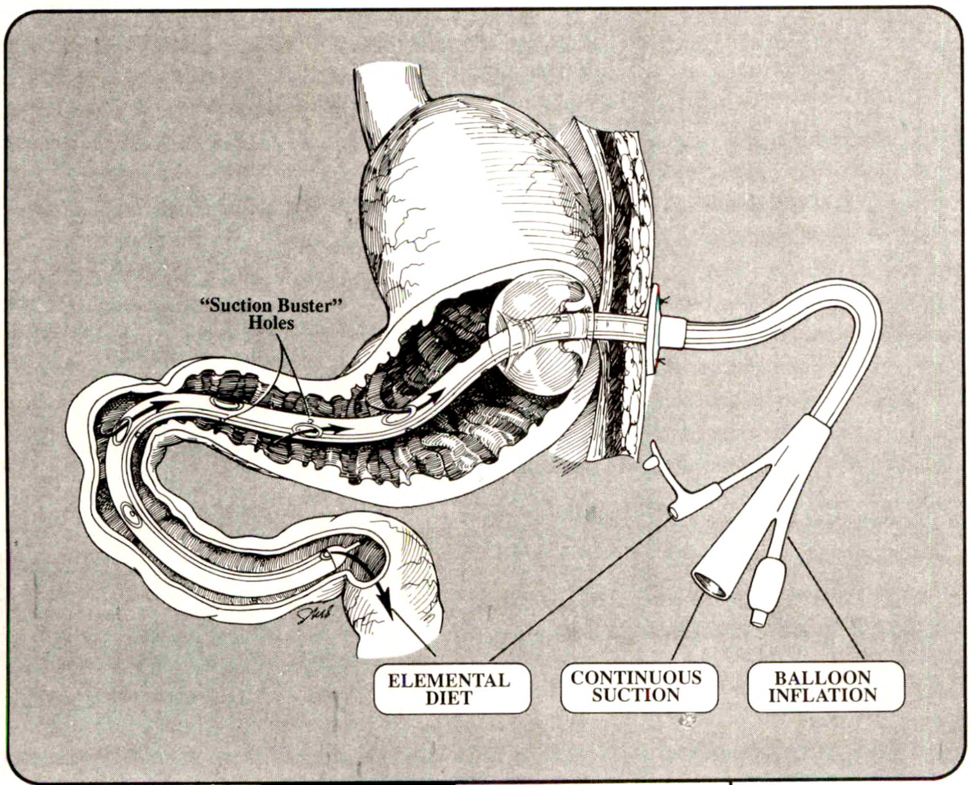

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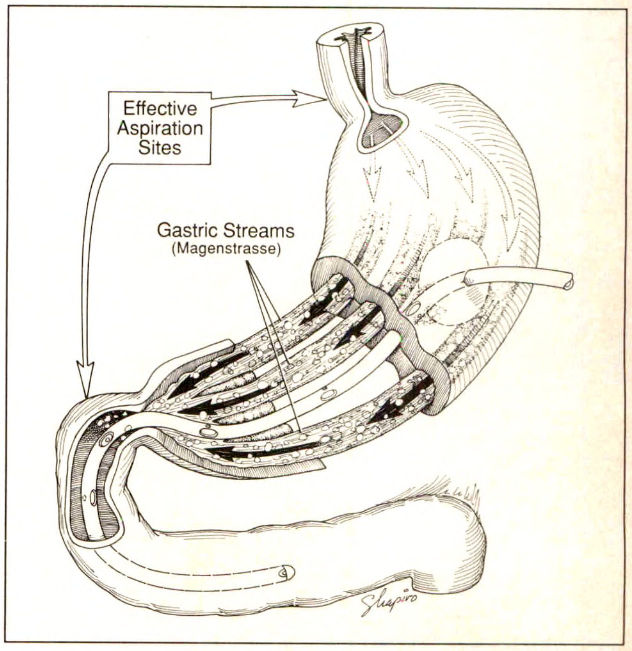

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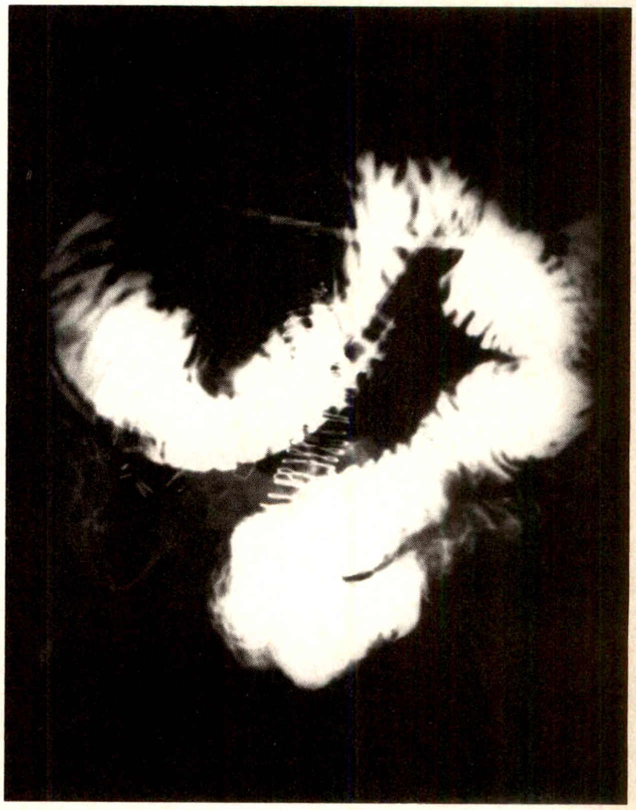

B. Study @ 5 minutes. Note effective removal of all excess barium flowing retrograde, none visualized to reach the stomach.

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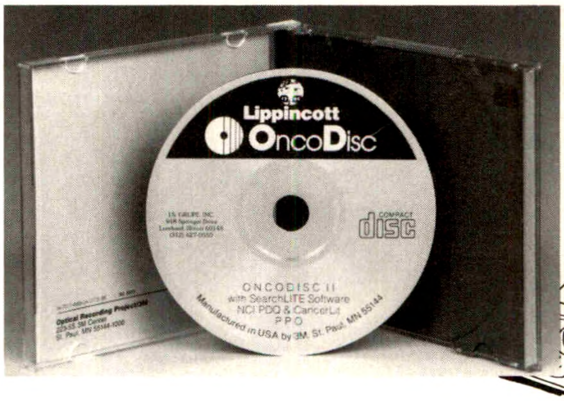

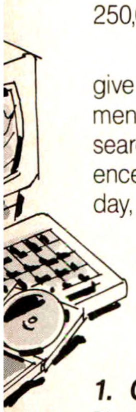

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An Aggressive Entity

ANDREW L. WARSHAW, M.D., ASHBY C. MONCURE, M.D., and DAVID W. RATTNER, M.D.

Previous reports of gastrocutaneous fistulas emphasize their benign nature and the probability of spontaneous healing without the need for surgical closure. In distinct contrast we report our experiences with six patients whose gastrocutaneous fistulas were caused by fulminant pancreatitis and pancreatic abscesses. High-output acid fistulas appeared days to weeks after drainage of left upper quadrant-infected collections. None occurred at the time of initial abscess drainage. Most originated high on the greater curvature of the stomach and traversed the abscess cavity. Three of six patients had previous splenectomies, but these operations were remote in time from the appearance of the fistula. Nonoperative management was successful in only two of six patients. Massive hemorrhage from the fistula tract contributed to the deaths of three patients. The pathogenesis of these fistulas appears to be consequent to gastric injury resulting from adjacent pancreatic inflammation. We conclude that (1) gastrocutaneous fistulas associated with pancreatitis are unlikely to heal even with drainage of the abscesses and are often complicated by hemorrhage, (2) surgical closure of the fistula will often be necessary and should not be unreasonably delayed, and (3) when performed in a semi-elective setting, resection of the damaged gastric segment, perhaps with an omental or serosal patch to buttress the gastric suture line, has a good chance of success.

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THE DEVELOPMENT OF EXTERNAL fistulas after acute pancreatitis is well recognized. Most fistulas arise from the pancreatic ductal system, often after debridement of pancreatic necrosis or external drainage of pancreatic pseudocysts. Colocutaneous fistulas are the second most frequently encountered and are thought to be due to ischemic necrosis of the bowel.[1,2] In contrast gastrocutaneous fistulas arising as a consequence of severe pancreatitis have not been widely appreciated or considered as an entity.

Most gastrocutaneous fistulas occur after iatrogenic gastric injury (particularly after splenectomy), breakdown of a gastroenteric anastomosis, or failure of healing of a gastrostomy tube tract.[3,4] Previous reports emphasize the benign nature of gastrocutaneous fistulas and the probability of spontaneous healing without surgical intervention.[3-6] We encountered six cases of gastrocutaneous fistulas arising as a consequence of pancreatic abscesses over a 12-year period. These fistulas responded poorly to nonoperative management and were associated with a 50% incidence of life-threatening hemorrhage from the fistula tract. To our knowledge, this is the first report specifically addressing the association of gastrocutaneous fistulas with pancreatic abscesses.

Materials and Methods

We identified six cases of gastrocutaneous fistulas associated with pancreatic abscesses in our practice at the Massachusetts General Hospital. Gastrocutaneous fistulas originating at the site of a previous gastrostomy, developing as a complication of a primary gastric or splenic procedure, or as a complication of radiation therapy were excluded. Both the office and hospital records of all patients were available for review. Follow-up until death or fistula closure was complete in all patients.

Results

Incidence

Six patients were identified with gastrocutaneous fistulas complicating pancreatic abscesses in 12 years. During the period of this study, approximately 130 cases of pancreatitis and four to five pancreatic abscesses were treated each year at the Massachusetts General Hospital. Five of the patients were men. The patients ranged in age from 24 to 78 years, with a mean age of 49 years.

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Presentation

All patients had severe acute pancreatitis. Pancreatitis was caused by gallstones in 3 cases, trauma in 2 cases (1 motor vehicle accident with blunt abdominal trauma, and 1 operative injury to the pancreas), and alcohol in 1 case. The appearance of a gastrocutaneous fistula was noted between 6 and 9 weeks (average, 7.5 weeks) from the onset of pancreatitis in all patients. Before the recognition of a gastrocutaneous fistula, all patients had surgical drainage of a pancreatic abscess. Five of the six abscesses were localized in the retroperitoneal left upper quadrant and the other was a large lesser sac collection. No gastric injury or gastric fistula was apparent at the time of the initial abscess drainage. The diagnosis was generally made days to weeks later by a sudden increase in the amount of drainage appearing *via* the drain tract or by the development of a recurrent abscess in the left upper quadrant. The drainage fluid in all cases was acid (pH < 2). The clinical diagnosis was confirmed by upper GI series in four patients and by fistulogram in two patients (Figs. 1 and 2).

In two patients with severe pancreatitis, the pancreatic abscess was also associated with colonic infarction or perforation. A transverse colostomy was performed at the time of drainage of the abscess in these patients, and subsequent radiologic studies demonstrated gastrocolocutaneous fistulas (Fig. 3).

Three patients had splenectomies before the development of gastrocutaneous fistulas. The indications for splenectomy were splenic rupture due to blunt trauma, operative injury to the spleen during colonic resection, and splenic infarction due to severe necrotizing pancreatitis. Splenectomies were performed in these patients 5 to 9 weeks before the development of gastrocutaneous fistulas.

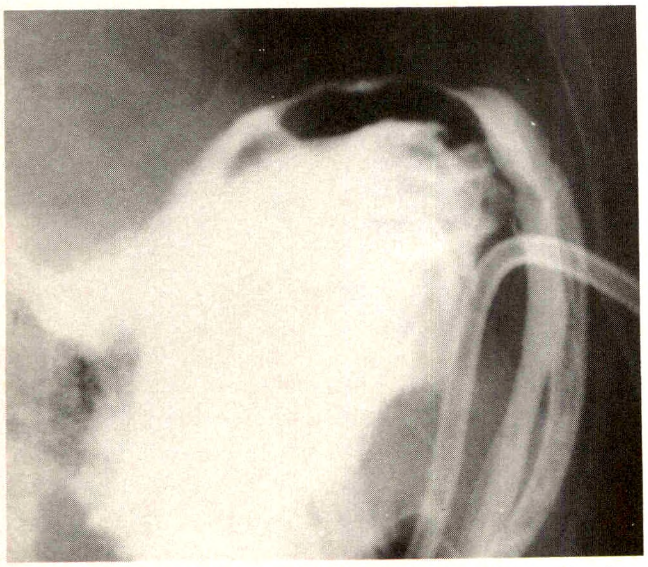
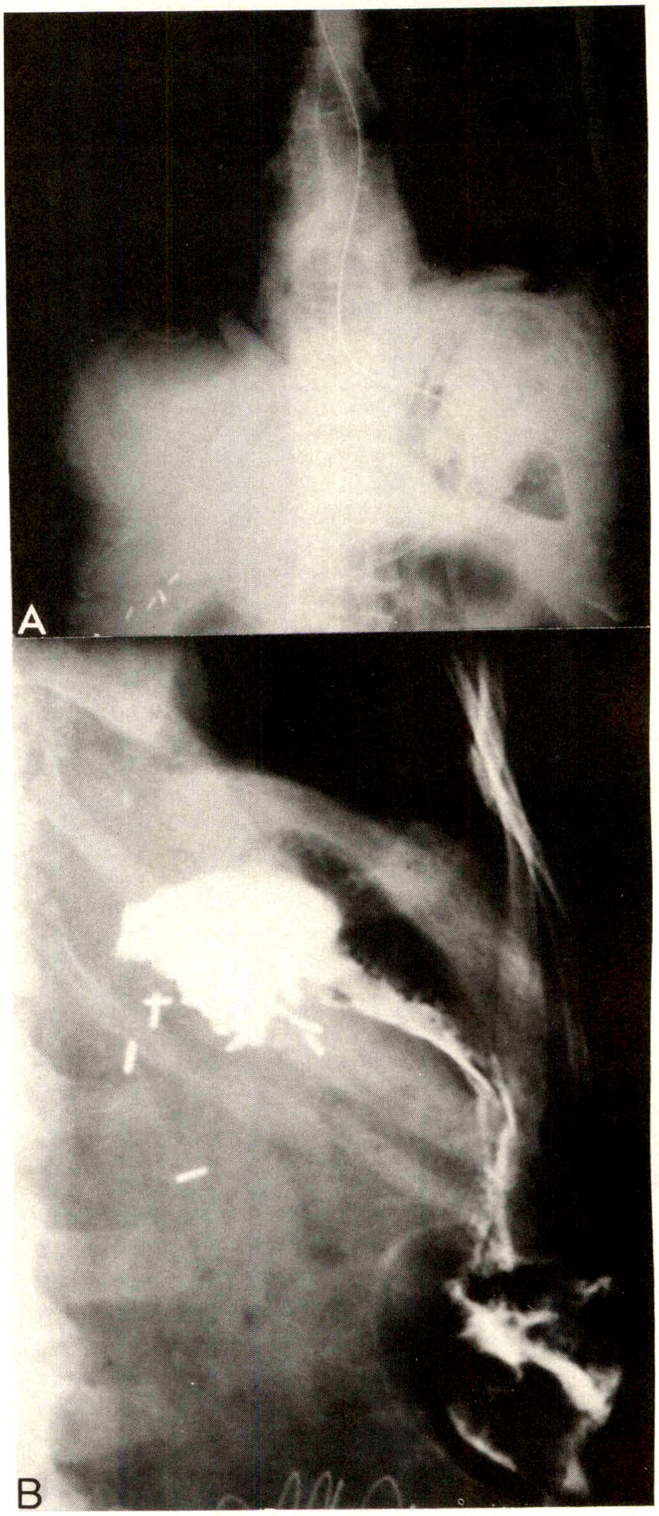


FIG. 1. Upper gastrointestinal series demonstrating barium leaking from the greater curvature of the gastric fundus.



FIGS. 2A and B. (A) Abdominal roentgenogram demonstrating a mottled density behind the stomach, consistent with pancreatic necrosis and abscess. (B) Fistulogram from the same patient 2 weeks after drainage of the subphrenic abscess. The fistula originates high on the greater curvature of the stomach.

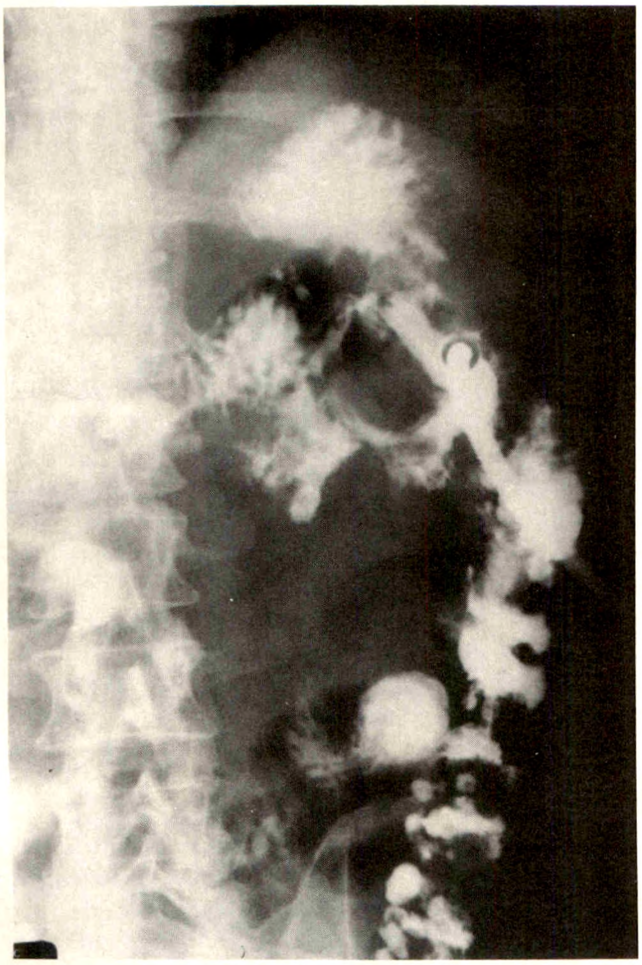


FIG. 3. Fistulogram demonstrating a gastrocolocutaneous fistula after drainage of a pancreatic abscess. The drain sits in the abscess cavity between the splenic flexure and the stomach. Fecal drainage had been noted, but the communication with the stomach was not appreciated before this study.

Soft rubber drains were in the bed of abscess cavities near the stomach in four of six cases at the time the fistula was diagnosed.

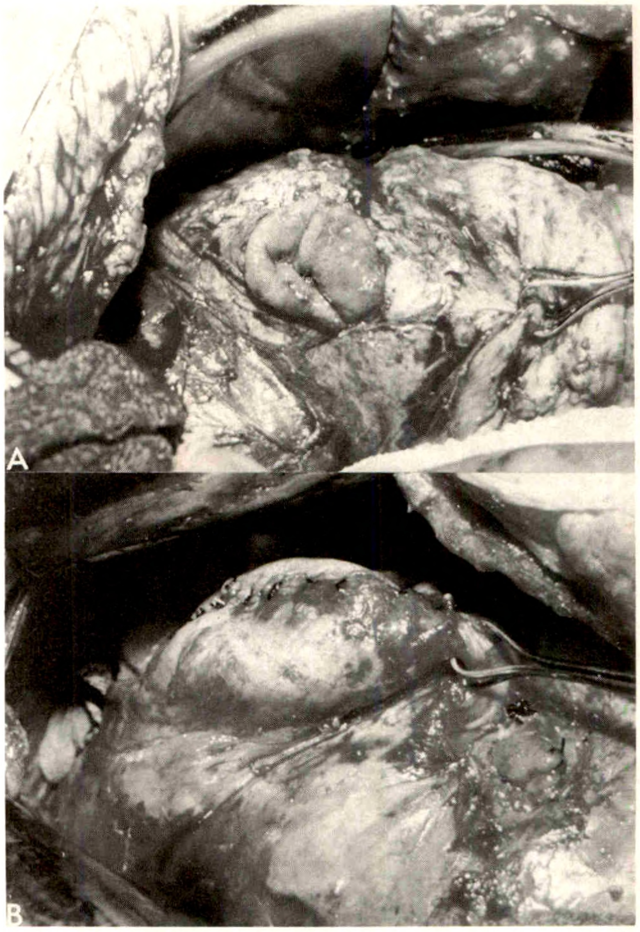
Complications

All patients had a complex clinical course with signs of undrained sepsis at the time the gastrocutaneous fistula was recognized. The most striking complication was massive hemorrhage from the fistula tract in three of six patients. All of these patients required transfusion of more than 10 units of blood in a 48-hour period and all manifested hemodynamic evidence of hypovolemia. Two other patients had bloody drainage from the fistula at some point in their illness, but no hemodynamically significant bleeding.

Outcome

The three patients with massive hemorrhage from the fistula required urgent angiographic and surgical intervention. All of these three patients ultimately died. One of these patients sustained an iatrogenic dissection of the celiac axis during attempted angiographic embolization of the bleeding site. This led to infarction of the upper abdominal viscera and death. In another patient who was 78 years old, hypotension caused by hemorrhage led to a perioperative myocardial infarction and death on the third postoperative day. The third patient with massive hemorrhage had successful surgical closure of the gastrocutaneous fistula and control of bleeding but died of persistent sepsis 2 weeks after operation. Surgical closure of the gastrocutaneous fistula was also successfully performed in a semi-elective setting in one other patient (Figs. 4A and B).

Both patients with gastrocolocutaneous fistulas were successfully treated by drainage of the abscess cavity and proximal colostomy for fecal diversion, but without direct surgical closure of the gastric defect. The gastric fistulas subsequently closed in 3 and 4 months, respectively. One patient whose barium enema showed closure of the colonic fistula had his transverse colostomy closed, and the



FIGS. 4A and B. Intraoperative photograph showing the gastric fistula after mobilization of the greater curvature. (B) Completed three-layer closure of the gastric perforation.

TABLE 1. *Characteristics of Patients with Gastrocutaneous Fistulas*

Patient	Age	Cause of Pancreatitis	Splenectomy	Colonic Fistula	Hemorrhage	Mortality
1	24	Blunt trauma	+	+		
2	78	Biliary			+	+
3	68	Operative trauma	+		+	+
4	47	Alcohol	+			
5	61	Biliary		+		
6	62	Biliary			+	+

other patient underwent an elective left colectomy 3 months after recovering from his acute illness (Table 1).

Discussion

Previous reports have emphasized the relatively benign nature of gastrocutaneous fistulas and the success of nonoperative management.[3,6] However no previous report has discussed the development of gastrocutaneous fistulas in the setting of pancreatic abscesses. In contrast to gastrocutaneous fistulas arising from other causes, gastrocutaneous fistulas secondary to pancreatic abscesses are life threatening, as evidenced by the 50% mortality rate in this series.

The pathogenesis of these fistulas is uncertain and may be multifactorial. Because all patients had previous surgery in the left upper quadrant, the role of iatrogenic injury to the stomach cannot be dismissed, in particular the potential for ischemic necrosis of the greater curvature after splenectomy.[3,4] Although three patients in this series had splenectomies before the development of the fistula, three others did not and thus iatrogenic gastric injury after splenectomy cannot fully account for the findings. External drainage catheters lying adjacent to the stomach for prolonged periods of time are believed to be capable of eroding the gastric wall with subsequent gastrocutaneous fistula formation.[6] In four cases in this series, erosion of the stomach by drainage catheters may have contributed to the pathogenesis of the fistula, notwithstanding that only soft rubber drains were used. Two patients no longer had indwelling drains when the fistula appeared, however. The only common denominator among all patients was ongoing active pancreatic inflammation. Vascular thrombosis is well known within areas affected by severe pancreatitis, perhaps due to the action of liberated enzymes on blood vessels, and may have caused ischemic necrosis of the gastric wall.[7] The simultaneous occurrence of colonic necrosis and fistulas in two of the six patients supports this hypothesis.[1,2]

In addition to producing vascular thrombosis, activated pancreatic enzymes may have the power to penetrate visceral walls directly. The propensity for pancreatic pseudocysts to decompress spontaneously by erosion into adjacent viscera is well known.[8] Apparently pancreatic abscesses can behave in a similar fashion.[9] A recent report documented spontaneous erosion of the stomach by a pancreatic abscess.[10] The internal fistula in that case originated high on the greater curvature of the stomach similar to the cases described in this report (Fig. 1).

Hemorrhage is a recognized complication of both pancreatic pseudocysts and abscesses.[11,12] Pancreatic enzymes, especially elastase, may digest blood vessel walls to produce pseudoaneurysms and rupture. The acidity of the fistula contents may further contribute to ulceration of the walls and blood vessels along the fistula tract. Because the stomach has a particularly rich blood supply, massive life-threatening bleeding from gastric fistulas associated with pancreatic abscesses is predictably common, occurring in one half of our patients. Although the gravity of bleeding associated with pancreatic abscesses has been noteworthy,[11-13] hemorrhage from eroded blood vessels can be arrested in most cases by angiographic embolization, and surgical resection and reconstruction of damaged viscera can then be performed under more controlled conditions.[11] Adjunctive treatment of this sort has reduced the number of deaths from pancreatic abscesses and infected necrosis to as little as 5%.[12]

During this same study period, we have treated three patients with duodenocutaneous fistulas associated with pancreatic abscesses. Somewhat to our surprise, all three of the duodenal holes healed without complication under conservative management. This apparently different behavior may indicate the deleterious role of unbuffered acid drainage from a gastric fistula, in contrast to the duodenal contents that contain alkaline bile and pancreatic secretions. The different behavior of acid and alkaline fistulas is further exemplified by a contemporaneous patient with a pancreatic abscess whose gastrocutaneous fistula resulted from a dehisced gastrostomy. That patient also experienced a high-output acid fistula, developed massive bleeding through the fistula, and ultimately was salvaged only by re-exploration and successful closure of the gastric defect.

While some gastrocutaneous fistulas associated with pancreatic abscess will heal, our experience illustrates that the risk of further complications, especially bleeding and uncontrolled sepsis, is a constant threat, greater than that from fistulas located elsewhere along the gut.[12] A trial of nonoperative therapy consisting of H_2-blockers and nasogastric suction may be worthwhile, but specific time limits, probably no longer than a few weeks, should be set. Continuing high output from the fistula seems to indicate a low probability of healing. Limited resection of the damaged gastric segment and direct closure in two or three layers, buttressed with omentum, when possible, or with a serosal patch, has been successful.

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The Spectrum and Natural History of Common Bile Duct Stenosis in Chronic Alcohol-Induced Pancreatitis

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Sixty patients with chronic alcohol-induced pancreatitis with endoscopic retrograde cholangiopancreatography evidence of common bile duct stenosis were studied to determine the clinical spectrum and natural history of this complication, as well as the indications for biliary bypass. In 17% of patients, common bile duct stenosis (CBDS) was an incidental finding at ERCP, while in the remaining cases pain and jaundice were the predominant symptoms in 35% and 48%, respectively. Biliary drainage was performed in 38% of patients for persistent or recurrent jaundice, cholangitis, and while undergoing pancreatic duct or cyst drainage procedures for pain. The benign nature of CBDS in chronic alcohol-induced pancreatitis (CAIP) in patients without persistent jaundice is emphasized. In particular, no histologically proved cases of secondary biliary cirrhosis were noted. The majority of patients with CBDS due to CAIP may be safely managed without biliary bypass but require close follow-up.

THE LOWER COMMON bile duct transverses pancreatic tissue in most patients[1] and thus may become narrowed in neoplasms or inflammatory disorders of the pancreas. Common bile duct stenosis (CBDS) in association with pancreatitis may be due to edema, pseudocyst formation, progressive encasement by pancreatic fibrosis, or pancreatic carcinoma. A spectrum of clinical diseases associated with CBDS has been well documented,[2–8] but the long-term natural history of this complication has not been fully evaluated. The aim of this study was to report our experience with CBDS in a large series of patients with chronic alcohol-induced pancreatitis (CAIP), emphasizing the spectrum of the disease, its natural history, and the indications for surgical biliary drainage.

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Clinical Materials and Methods

Sixty patients with CAIP associated with benign CBDS were identified from endoscopic retrograde cholangiopancreatography (ERCP) records for the 7-year period from 1979 to 1985. In addition the diagnosis of chronic pancreatitis was established by one or more of the following criteria: pancreatic calcification, impaired pancreatic response to secretin/pancreozymin stimulation, and diagnostic confirmation at laparotomy. Relevant clinical, biochemical, radiologic, and liver histopathologic features were extracted from patient records. Biliary strictures were categorized from endoscopic cholangiography according to recognized criteria.[5,9] Indications for surgical biliary decompression and long-term follow-up of patients treated by surgery or by nonsurgical management were noted. Statistical comparisons were made using the Student's t test or chi squared test when appropriate.

Results

The diagnosis of CBDS was made by ERCP at an mean interval of 8 years after the onset of abdominal pain (range, 0 to 19 years). There were 56 men and 4 women with mean age at diagnosis of CBDS of 44 years (range, 25 to 65 years).

The patients were classified into three arbitrary groups according to their respective dominant clinical presentations: group 1 (10 patients, asymptomatic or minimally symptomatic); group 2 (21 patients, significant epigastric abdominal pain); group 3 (29 patients, jaundice with or without cholangitis). Comparative data for the individual groups is given in Table 1.

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TABLE 1. *Clinical Data for Patients with CBDS According to Initial Presentation*

Group (No. of Patients)	Group 1 (10) (asymptomatic)	Group 2 (21) (pain)	Group 3 (29) (jaundice)	Significance Levels
Age (years) at diagnosis of CBDS (mean) (range)	46 (28–59)	41 (25–58)	43 (26–65)	
Pancreatic calcification	8 (80%)	17 (81%)	29 (100%)	1 + 2 *vs.* 3 $p < 0.005$
Impaired glucose tolerance or diabetes	6 (60%)	8/16 (50%)	17/20 (85%)	1 + 2 *vs.* 3 $p < 0.05$
Steatorrhea (%)	6 (60%)	6/13 (46%)	14/17 (82%)	1 + 2 *vs.* 3 $p < 0.05$

CBDS, common bile duct stenosis.

Patients in group 3 had a significantly higher frequency of pancreatic calcification ($p < 0.005$), diabetes mellitus or impaired glucose intolerance ($p < 0.05$), and steatorrhea ($p < 0.05$) than did patients in groups 1 and 2 combined.

During the total follow-up period of the study (January 1979 to January 1986), 23 patients (38%) underwent surgical biliary drainage—none from group 1, 6 from group 2 (29%), and 17 from group 3 (59%). The bile duct was drained into the duodenum in 13 patients and into the jejunum in the remaining ten. Biochemical data at initial presentation and at last follow-up visit for patients treated with biliary drainage and those treated without drainage, respectively, are given in Table 2. Alkaline phosphatase (AP) and total serum bilirubin (TSB) levels at presentation were significantly higher ($p < 0.02$ and $p < 0.001$, respectively) in group 3 than in groups 1 and 2 combined. However a wide range of values within each group and marked overlap of values between groups were observed. Both AP and TSB were invariably elevated in group 3 patients. Significant elevation in AP with normal TSB was seen in 5 group 1 patients, 9 group 2 patients, and no group 3 patients. Although patients who underwent biliary drainage had significantly higher mean AP levels (571U *vs.* 302IU; $p < 0.01$) and TSB levels (100μmol/l *vs.* 33μmol/l; $p < 0.05$), than those treated conservatively, marked overlap of values was noted.

TABLE 2. *Biochemical Data for Patients with CBDS*

A. No Biliary Drainage (37 patients)

Group (No. of Patients)	1 (10)	2 (15)	3 (12)	Significance Levels
Alkaline Phosphatase ($\bar{x} \pm$ SEM) (normal < 115IU)				
Initial level	290 ± 103	182 ± 49	465 ± 96	1 + 2 *vs.* 3 $p < 0.02$
Last follow-up level	272 ± 92	157 ± 32	195 ± 63	1 + 2 *vs.* 3 NS
	NS	NS	NS	
Total Serum Bilirubin ($\bar{x} \pm$ SEM) (normal < 17 μmol/l)				
Initial level	9 ± 2	13 ± 4	79 ± 38	1 + 2 *vs.* 3 $p < 0.001$
Last follow-up level	7 ± 2	13 ± 3	27 ± 13	1 + 2 *vs.* 3 NS
	NS	NS	NS	

B. Biliary Drainage (23 patients)

Group (No. of Patients)	1 (0)	2 (6)	3 (17)	Significance Levels
Alkaline Phosphatase				
Initial visit	—	382 ± 111	638 ± 86	NS
Last follow-up level	—	166 ± 24	137 ± 13	NS
		NS	$p < 0.001$	
Total Serum Bilirubin				
Initial level	—	10 ± 2	133 ± 27	$p < 0.02$
Last follow-up level	—	10 ± 2	13 ± 3	NS
		NS	$p < 0.001$	

NS, not significantly different.

TABLE 3. *Radiologic Data for Patients with CBDS*

Group (No. of Patients)	1 (10)	2 (21)	3 (29)	Significance Levels
Stricture type (1/2/3/4)	8/0/2/0	16/1/3/1	21/3/4/1	
Biliary dilatation	2 (20%)	6 (29%)	21 (72%)	1 + 2 *vs.* 3 $p < 0.005$
CBD calculi	0	0	4 (14%)	
Pancreatic pseudocysts	1 (10%)	9 (43%)	4 (14%)	

Radiologic data are shown in Table 3 and examples of stricture types are shown in Figures 1 to 3. The majority of patients exhibited type 1 or type 3 strictures, and there were no significant differences between the three groups in stricture type. However extrahepatic biliary dilatation (CBD diameter >10 mm) with or without intrahepatic dilatation was present in significantly more group 3 patients than groups 1 and 2 combined ($p < 0.005$) and was also significantly more frequent ($p < 0.01$) in patients who had biliary drainage (21 of 23) than in patients treated without drainage (8 of 37). Choledocholithiasis was found in four group 3 patients.

Twenty-nine patients underwent liver biopsy during the follow-up period (Table 4). Histologic evidence of extrahepatic biliary obstruction (EHBO)[10] was present in almost one half of the biopsies, but was significantly more frequent ($p < 0.05$) in group 3 patients when compared with groups 1 and 2. There were no cases of secondary biliary cirrhosis. EHBO was noted more frequently in patients treated with biliary decompression (11 of 18) than in patients treated without surgery (3 of 11), but the difference was not statistically significant.

Biliary drainage was not performed in any group 1 patients. Nine of ten patients in this group were asymptomatic at a mean follow-up time of 46 months after diagnosis of CBDS, and one had died of problems unrelated to his biliary tract. The mean AP and TSB levels remained unchanged during the follow-up period (Table 2).

Six group 2 patients had biliary drainage surgery in addition to a longitudinal pancreaticojejunostomy in five and pancreatic cystojejunostomy in one. In these patients, pancreatic drainage for pain was the primary indication for surgery, and the bile duct was drained concomitantly. At last follow-up, all six patients had done well in terms

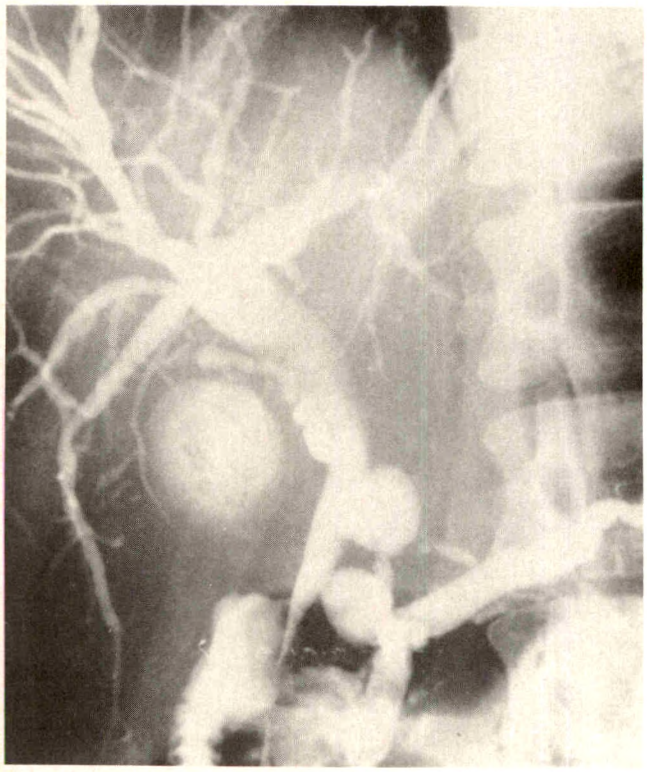

FIG. 1. Gradual tapering of the distal common bile duct (type 1 stricture) in a 40-year-old patient with chronic calcific pancreatitis, pseudocysts in the head of the pancreas, and gallstones.

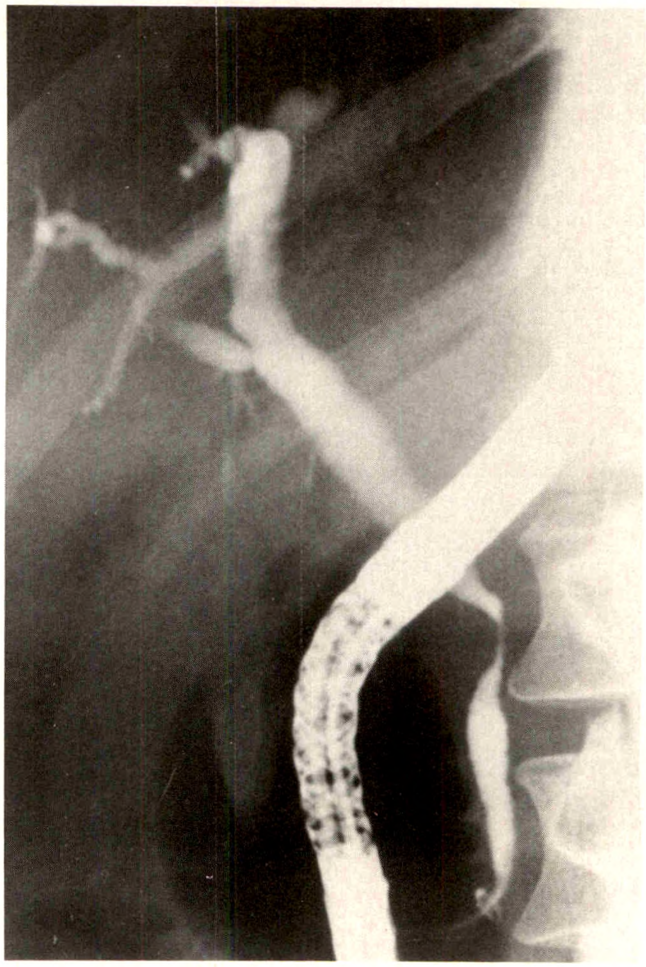

FIG. 2. Abrupt "birds-beak" stenosis (type 2) of the distal common bile duct in a 45-year-old patient with severe chronic calcific pancreatitis. A calcified hydatid cyst in the right lobe of the liver is also present.

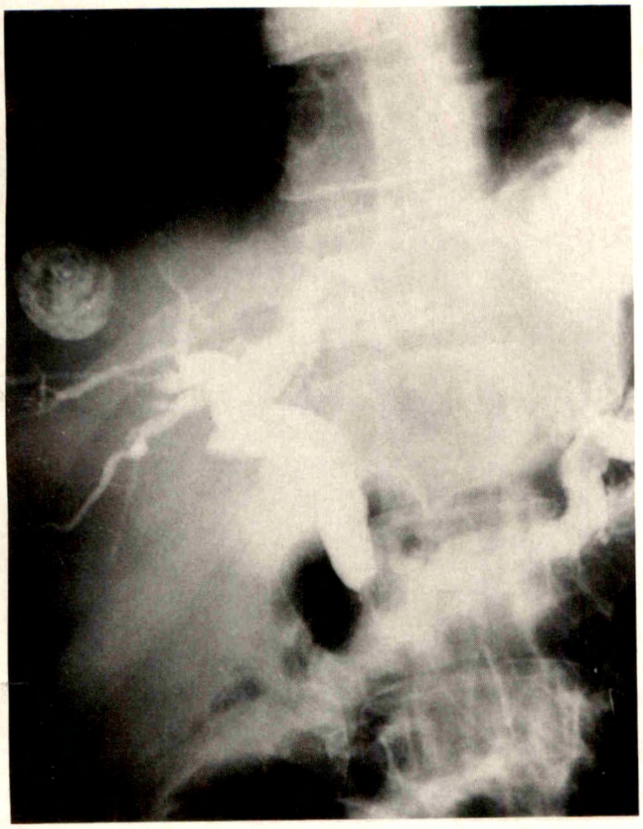

FIG. 3. Type 3 ("hour-glass") stricture of the mid-portion of the common bile duct. This 39-year-old patient had chronic noncalcific pancreatitis.

of their biliary tract (mean follow-up, 43 months), but two had persistent pain. Of the 15 nonoperated patients, 6 of 10 for whom follow-up data were available were well at a mean interval of 29 months from diagnosis of CBDS. Persistent pain was the main problem in the remaining four patients. Nonsignificant mean AP reduction was noted in the patients who underwent biliary drainage and in the nonoperated patients.

Of 29 patients who presented with jaundice as the primary clinical problem, 17 (59%) initially improved with nonoperative treatment. However, five of these subjects, together with the remaining 12 who had persistent jaundice, underwent biliary bypass. Mean AP and TSB levels were not significantly different between group 3 patients undergoing biliary bypass and those treated without bypass, although there was a trend toward higher levels in the surgical patients (Table 2). The indications for surgery were jaundice in 13 patients, jaundice and cholangitis in 3, and jaundice and pain in 1 (on whom a concomitant pancreatic drainage procedure was performed). One patient died after operation of ischemic heart disease, 1 patient subsequently died of cardiac complications after a Puestow procedure, 2 have persistent pancreatic pain, and 2 have been lost to follow-up. The remaining 11 patients were well at a mean follow-up of 35 months. Mean AP and TSB levels were significantly improved in group 3 patients who underwent biliary drainage (Table 2B). Biliary drainage was not performed in 12 patients with jaundice, most of whom had transient hyperbilirubinemia that lasted less than 1 month. Two have died subsequently (one cerebrovascular accident, and one diabetic patient after pancreatic cystoenterostomy complicated by sepsis), one has undergone Whipple's procedure for persistent pancreatic pain, and three have been lost to follow-up. Six patients were well at their last follow-up visit, at a mean interval of 26 months from diagnosis. A trend toward improved AP and TSB levels in nonoperated patients was observed (Table 2A).

Follow-up data were available in 29 of 37 patients managed without biliary drainage. Twenty-one of 29 patients (72%) were asymptomatic at their last follow-up. No patients had significant clinical biliary tract problems. Both AP and TSB levels showed a nonsignificant downward trend in each group, and values for groups 1 and 2 combined were no longer significantly different from group 3 (Table 2A).

The overall result of surgery was satisfactory in terms of the biliary system in 20 of 21 patients (95%) for whom follow-up data were available. Five of 20 patients (25%) who survived surgery have either died (1 patient) or have ongoing pancreatic pain (4 patients). Mean AP and TSB levels at last follow-up were significantly improved over preoperative levels and were not significantly different between groups (Table 2B).

Discussion

With the advent of modern imaging techniques, in particular ERCP, CBDS is now a frequent finding in patients with CAIP.[5,11-14] This complication appears to be more common in the advanced calcific form of the disease.[13] It may manifest as an incidental finding on ERCP or an isolated elevation of AP, or present with pain or jaundice with or without cholangitis.[2-8] The risk of developing secondary biliary cirrhosis has been stressed in many studies[4,15-18] but has been questioned by others.[5,13,19] The natural history of this condition is influenced by numerous factors, including reversible pancreatic edema or pseudocyst formation during acute relapses, and progressive

TABLE 4. *Histopathologic Date for Patients with CBDS*

Group (No. of Biopsies)	1 (6)	2 (8)	3 (15)	Significance Levels
Normal	2 (33%)	2 (25%)	2 (13%)	
EHBO	2 (33%)	2 (25%)	10 (67%)	1 + 2 *vs.* 3 $p < 0.05$
Secondary Biliary Cirrhosis	0	0	0	
Alcoholic liver disease	1 (17%)	2 (25%)	2 (13%)	
Nonspecific changes	1 (17%)	2 (25%)	1 (7%)	

and irreversible pancreatic fibrosis and calcification during the end stage of the disease. Consequently planning a rational treatment strategy in a given patient has been difficult.

The incidental finding of CBD abnormalities in asymptomatic patients with or without an elevated AP is well recognized[2,5–7,14] and constituted 17% in this series. While a continued conservative approach would seem appropriate in relatively asymptomatic patients with a normal or minimally raised AP, many authors stress the need for a prophylactic biliary drainage procedure in those with a more markedly raised AP, hyperbilirubinemia not associated with alcoholic liver disease, and persistent or progressive CBDS in the absence of acute pancreatitis because of the perceived risk of cholangitis or secondary biliary cirrhosis.[4,6,7,15–18] In this study, however, most patients in this category were treated without biliary drainage, including those with disproportionate AP elevation. These patients have remained well over a follow-up period of up to 4 years without developing jaundice or secondary biliary cirrhosis, which is in keeping with the experience of others.[5,13,18,19] Although the mean AP level remains elevated, a trend toward improvement was noted. Our results to date are in keeping with the finding that the risk of secondary biliary cirrhosis is low in such patients.[5,13,14,19]

The second largest group of patients with CBDS in this study presented with pain as the predominant clinical feature. Although pain relief after biliary diversion has been documented,[4] we concur with others that the pain is more likely to be pancreatic in origin[8,17,20–22] unless there are associated biliary calculi. All the biliary drainage procedures in this group were performed in conjunction with drainage of a pseudocyst or dilated pancreatic duct. As in our asymptomatic group, patients not operated on did not develop biliary complications during a median follow-up period of almost 2.5 years and showed a trend toward reduced AP levels.

Extrahepatic cholestasis in chronic pancreatitis is frequently self-limiting due to transient edematous inflammation or resolution of a pseudocyst in the head of the pancreas.[5–7,12–14,19,20,23,24] Of 29 patients who presented with jaundice in this study more than one half initially improved and only five of them underwent biliary bypass at a later stage. Abstinence from alcohol may have played an important role, but reliable information was not available to substantiate this. Although histologic evidence of extrahepatic biliary obstruction was evident in two thirds of liver biopsies in patients with transient or recurrent jaundice at variable points in their clinical course, no case of secondary biliary cirrhosis was noted even in patients with persistent jaundice.

The timing of surgery in patients with jaundice due to CBDS is uncertain, but it seems reasonable to adopt an expectant policy for 2 to 3 weeks, awaiting spontaneous resolution. However in the presence of choledocholithiasis, cholangitis, or recurrent jaundice, early biliary decompression is indicated, particularly in the absence of recent alcohol ingestion. In all cases, assessment for surgery should include noninvasive radiology to identify pseudocysts that may cause reversible compression to the distal bile duct. Endoscopic or percutaneous cholangiography is mandatory to identify bile duct calculi, exclude carcinoma, and allow adequate surgical planning. In this regard, ERCP offers the added advantage of visualization of the pancreatic duct system. Preoperative liver biopsy may be warranted in some patients to assess the severity of liver damage from both extrahepatic obstruction and alcoholic liver disease. In patients considered to be definite candidates for biliary decompression, choledochoduodenostomy is preferable to choledochojejunostomy unless a Roux loop is required to drain a pseudocyst or when a pancreatic duct drainage procedure is needed.[8,17–19,20,23,25] Although pseudocyst drainage alone may relieve biliary obstruction, care should be taken not to overlook common bile duct stenosis due to pancreatic fibrosis. Intraoperative cholangiography should help to exclude this possibility.[23,25,26] Conversely biliary drainage should be considered in some patients in whom pancreatic surgery for pain is contemplated, particularly in the presence of significant biochemical and anatomic evidence of cholestasis.[22,27] Cholecystenterostomy or sphincteroplasty are inadequate procedures,[4,8,16–18,20] and permanent biliary stenting is inappropriate. Unnecessary biliary bypass procedures should be avoided because some patients present serious operative risks due to the presence of segmental portal hypertension and problems with malnutrition and brittle diabetes.

Complete resolution of jaundice and only minimal or mild common bile duct dilatation are reasonable prerequisites for conservative nonoperative therapy. Careful long-term observation of patients treated without biliary drainage should include serial estimations of AP and TSB, ultrasonography, ERCP, and perhaps liver biopsy. In addition, radionuclide cholescintigraphy may have a role in assessing the functional status of the biliary tree in these patients.[28]

This study stresses the limitations of clinical parameters and currently available investigations in determining the natural history of CBDS in CAIP. In the light of its relatively benign course, we would support the conservative approach followed by others.[7,13,14]

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Acute Pancreatitis and Normoamylasemia

Not an Uncommon Combination

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A consecutive series of 352 attacks of acute pancreatitis (AP) was studied prospectively in 318 patients. AP was ascertained by contrast-enhanced CT scan in all but four cases in which diagnosis was made at operation or autopsy. Sixty-seven of these cases (19%) had normal serum amylase levels on admission (*i.e.*, less than 160 IU/L, a limit that includes 99% of control values), a figure considerably higher than generally admitted. When compared to AP with elevated serum amylase, normoamylasemic pancreatitis was characterized by the following: (1) the prevalence of alcoholic etiology (58% *vs.* 33%, respectively, $p < 0.01$), (2) a greater number of previous attacks in alcoholic pancreatitis (0.7 *vs.* 0.4, $p < 0.01$); and (3) a longer duration of symptoms before admission (2.4 *vs.* 1.5 days, $p < 0.005$). In contrast AP did not appear to differ significantly in terms of CT findings, Ranson's score, and clinical course, when comparing normo- and hyperamylasemic patients, although there was a tendency for normoamylasemic patients to follow milder courses. Serum lipase was measured in 65 of these normoamylasemic cases and was found to be elevated in 44 (68%), thus increasing diagnostic sensitivity from 81% when amylase alone is used to 94% for both enzymes. A peritoneal tab was obtained in 44 cases: amylase concentration in the first liter of dialysate was greater than 160 IU/L in 24 cases (55%), and lipase was greater than 250 U/L in 31 cases (70%). Twelve of these 44 cases had low peritoneal fluid and plasma concentrations for both enzymes. Thus little gain in diagnostic sensitivity was obtained when adding peritoneal values (96%) to serum determinations. AP is not invariably associated with elevated serum amylase. Multiple factors may contribute to the absence of hyperamylasemia on admission, including a return to normal enzyme levels before hospitalization or the inability of inflamed pancreases to produce amylase. Approximately two thirds of cases with normal amylasemia were properly identified by serum lipase determinations. AP does not appear to behave differently when serum amylase is normal or elevated, and should therefore be submitted to similar therapeutic regimens in both conditions.

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DESPITE THE COMMON ADAGE that "a normal value of serum amylase is so rare in cases of acute pancreatitis (AP) that the diagnosis should be questioned,"[1] cases of unsuspected AP found at laparotomy or even at autopsy have been reported[2–7] and suggest that the disease can exist without elevated serum amylase levels.

The purpose of this prospective study is to define the incidence of AP with normal amylasemia on admission by the systematic use of contrast-enhanced CT scan, which represents to date the best imaging technique for the pancreas.[1,6–8] CT scan was performed within 36 hours in all patients *suspected* of having AP. Both groups, *i.e.*, AP with normal and elevated serum amylase, were compared in terms of etiology, number of previous attacks, duration of symptoms, prognostic CT grading, Ranson's score, and outcome. Other enzymatic determinations were considered to see if they could advantageously supplement fallacious serum amylase findings.

Patients and Methods

Between January 1984 and March 1988, 318 patients with AP were admitted to the Clinic of Digestive Surgery of the Geneva University Hospital: 294 patients sejourned once, 17 twice, and 7 three times or more, which totalled 352 attacks of AP. Excluded from this series are cases of established chronic pancreatitis according to the recent classifications[9,10] (*i.e.*, pancreatic calcifications, dilatation of the pancreatic duct, or evidence of exocrine pancreatic insufficiency) or cases of pancreatitis after surgical or endoscopic procedures on the pancreas.

The diagnosis of AP was established in all cases by contrast-enhanced CT scan performed within the initial 36 hours of hospitalization, except in four cases in which the diagnosis was not established before operation (in three) or autopsy (in one). CT was performed with a third-gen-

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eration Siemens scanner (Erlanger, FRG; 125kV; 230mAs; acquisition time, 4 seconds) after both intravenous and oral administration of contrast media. Eight millimeter sections were taken from the level of the diaphragm to the third lumbar vertebra or further down in the presence of abnormal findings. Diagnostic criteria for pancreatitis included a locally or diffusely enlarged pancreas. Enhancement was harmoniously decreased in edema, while phlegmon or necrosis appeared as heterogeneous avascular areas. Extrapancreatic spreads (EPS), when present, were analyzed in terms of density, extent, homogeneity, enhancement, and localization. In accordance with our previous report,[7] EPSs were defined as edematous or phlegmonous and three groups were considered: CT group I showed no phlegmonous EPS; CT group II showed phlegmonous EPS in one or two areas; and CT group III showed phlegmonous EPS in three areas or more.

A modified Ranson's prognostic score,[11] omitting serum LDH levels, was calculated in all but the four cases mentioned earlier and included the following criteria: age more than 55 years for men and more than 60 years for women; admission leucocyte count more than 16,000 cells/mm^3, glycemia more than 11.1 mmol/L, sGOT (AST) more than 120 IU/L; and during the subsequent 48 hours, hematocrit fall more than 10%, blood urea nitrogen increase more than 18 mmol/L, serum calcium less than 2 mmol/L, arterial oxygen pressure less than 8.4 kPa, base deficit more than 4 mmol/L, and fluid sequestration more than 6 L.

Clinical course was assessed in terms of severity and three groups were considered. Mild attacks (n = 220, 62%) evolved without complications other than pseudocyst(s) resolving spontaneously. Severe attacks (n = 101, 29%) developed local or systemic complications that required percutaneous CT-guided drainage, surgery, or intensive care; parenteral nutrition lasting for more than 15 days was also considered within this subgroup. Necrotizing pancreatitis was demonstrated at operation and/or autopsy in all cases resulting in death (n = 31, 9%).

Amylase was measured spectrophotometrically in serum and peritoneal fluid by a chromogenic assay using *p*-nitrophenol oligosaccharides (substrate Testomar, Behringwerke, Marburg, West Germany).[12] When plasma was lipemic, serial dilutions were used for amylase determination. Reference values for serum amylase ranged from 5 to 160 IU/L and included 99% of 178 controls.[13] Serum amylase was determined on admission and at least four times during the hospital stay. Serum and peritoneal lipase was determined by a turbidimetric method that assays trioleine degradation.[14] The reference values for lipasemia were 0 to 250 U/L. Serum lipase was measured on admission in all but two cases of normoamylasemic AP. Peritoneal amylase and lipase were determined in the first liter of dialysate (isotonic saline), which incubated for approximately 6 hours.

Four causes of AP were identified: biliary lithiasis confirmed by ultrasonography, CT scan and/or surgery; alcohol; postoperative causes; and idiopathic causes when no other cause could be found (Table 1).

Management of AP consisted of nasogastric suction and fluid replacement. Percutaneous peritoneal lavage using 12 to 24 L of isotonic saline per day was performed in all cases unless contraindicated by a previous laparotomy, the palpation of an abdominal mass, or an important dilatation of the transverse colon seen on a plain abdominal x-ray or CT scan.[15]

Chi square with Yates' correction or Fisher's exact test according to the sample size and other nonparametric tests were performed by using the SPSS-X package.[16]

Results

Pancreatitis with and Without Elevated Serum Amylase

Sixty-seven of the 352 attacks of AP (19%) had serum amylase values at admission of less than 160 IU/L. Fifty of these attacks occurred in men (75%) and 17 in women (25%), with ages ranging from 23 to 80 years (median age, 48.5 years; men 45 years, women 59 years). Within the hyperamylasemic group (n = 285), there were 160 men (56%) and 125 women (44%) ranging in age from 19 to 87 years (median age, 52 years; men 46 years, women 60 years).

Duration of symptoms before admission. Median duration of symptoms before admission was longer in cases of normoamylasemic AP than in hyperamylasemic AP: 2.4 days (4 hours to 16 days) *vs.* 1.5 days (1 hour to 12 days); ($p < 0.005$, Mann-Whitney test). The difference was more significant still if etiology was biliary (1.8 *vs.* 0.8 days; $p < 0.001$) rather than alcoholic (2.5 *vs.* 2 days; $p < 0.01$). All eight cases of normoamylasemic biliary pancreatitis with pain for more than two days before ad-

TABLE 1. *Etiology of Acute Pancreatitis*

Serum Amylase at Admission (n)	Alcoholism (%)	Biliary Lithiasis (%)	Postoperative (%)	Idiopathic (%)	Others* (%)
Normal (67)	39 (58)	12 (18)	4 (6)	10 (15)	2 (3)
Elevated (285)	93 (33)	107 (38)	14 (5)	65 (23)	6 (2)
Total (N = 352)	132 (38)	119 (34)	18 (5)	75 (21)	8 (2)

* The column "others" refers to rare etiologies such as hyperlipidemia, hypercalcemia, or ampullary diverticula.

mission had benign clinical courses and hospital stays shorter than ten days.

Etiology (Table 1). Alcohol was incriminated in 39 of the 67 attacks of normoamylasemic AP (58%) and nearly always affected men (35 of 39). Nine of these cases had suffered previously from similar episodes, while twelve others had presented documented bouts of AP. The number of similar previous episodes in these 39 cases of alcoholic pancreatitis averaged 0.7 (from 0 to 4 episodes). Biliary AP occurred in 12 instances (18%), 7 times in women and 5 times in men, and none of them suffered previously from pancreatitis. Hyperlipidemia was found in four attacks (7%), all associated with chronic alcohol abuse. In four other patients (6%), pancreatitis followed an abdominal extrapancreatic operation, while a fifth patient presented with an ampullary diverticulum. Finally the cause of AP was unclear in the remaining ten patients (15%), although elevated gamma GT levels suggest an alcoholic origin in five of them.

In the group of AP with elevated serum amylase, biliary lithiasis (107 of 285 patients, 38%) prevailed slightly over alcohol (93 of 285 patients, 33%). In the latter subgroup, 37 had experienced previous bouts of pancreatitis (an average number of 0.4 similar episode per case). Alcoholic AP was less frequent and the number of previous attacks was significantly lower in the hyperamylasemic group ($p < 0.05$, chi square and Mann-Whitney tests, respectively).

Prognosis according to CT scan and Ranson's Score and clinical course (Figs. 1 and 2). In both grading systems (*i.e.*, CT and Ranson's criteria), AP did not appear to differ whether amylase was elevated or not, although there was a tendency for normoamylasemic patients to follow a milder course.

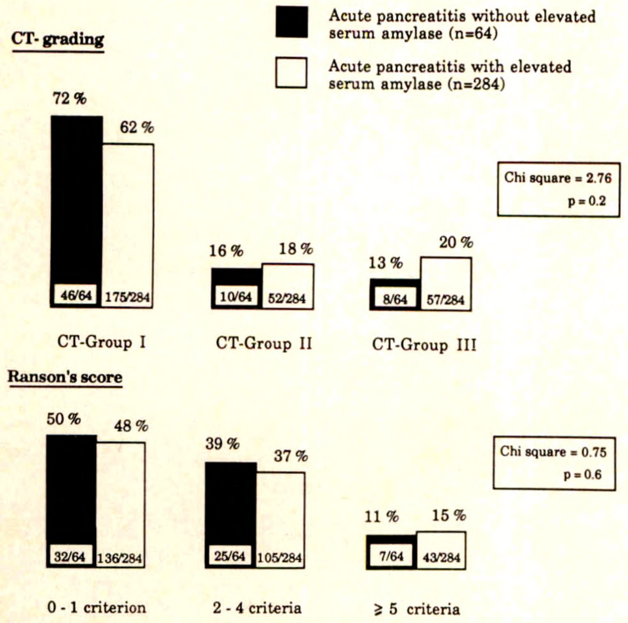


FIG. 1. CT grading and Ranson's score in 348 cases of acute pancreatitis with or without elevated serum amylase. Four cases had neither CT nor complete Ranson criteria because the diagnosis was not made before operation or autopsy.

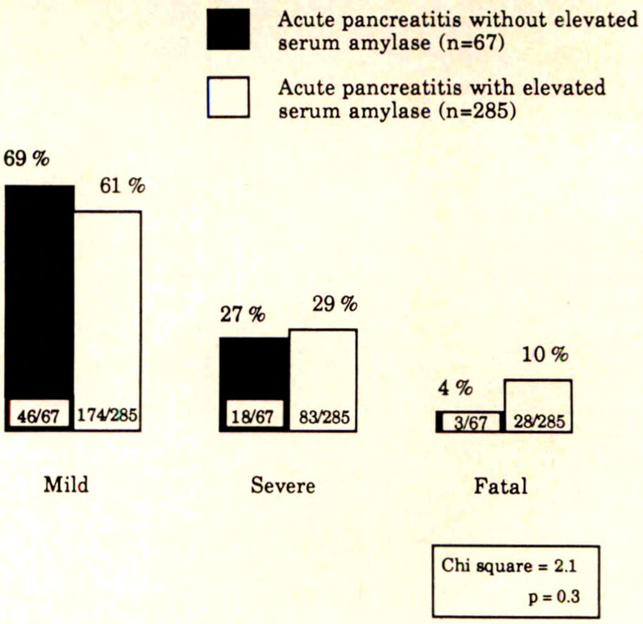


FIG. 2. Clinical course of 352 cases of acute pancreatitis with or without elevated serum amylase.

Forty-six of the 67 cases of AP with normal amylase (69%) had mild clinical courses. Nine of these developed pseudocysts that were diagnosed between the 8th and 42nd days of hospitalization and which all resolved spontaneously within 3 to 10 weeks.

Eighteen patients (27%) suffered complications. Four developed persistent pseudocysts treated by percutaneous CT-guided drainage alone (in three) or by duodenopancreatectomy (in one). Nine others developed symptomatic infected necrosis requiring laparostomy, necrosectomy, and lavage in eight, and lombostomy in one. Five more suffered systemic complications including multiple organ failure in 2, respiratory failure in 1, renal failure in 1, and severe denutrition in 1. Finally three patients (4%) whose history is described below had fatal outcomes.

A 74-year-old alcoholic man with no history of previous pancreatitis suffered from crampy abdominal pain and vomiting of one-day duration. Examination revealed guarding and slight tenderness of the lower abdomen. White cell count was 22×10^9 /L, serum amylase was 110 IU/L, serum lipase was 200 U/L, and urinary amylase was 50 IU/L. Diagnosis was assumed to be acute diverticulitis. CT scan revealed benign pancreatitis (CT group I) and Ranson's score was 3. No peritoneal dialysis was performed because of a previous laparotomy. He was transferred to the intensive care unit three days later because of respiratory failure. A second CT scan showed a worsening of his pancreatitis. During the following week, multiple organ failure with sepsis developed. Phlegmonous EPS was demonstrated on the third CT scan and the patient was operated on: necrosectomy (50 g), cholecystectomy, and jejunostomy brought about a transitory amelioration, although hemodialysis had to be started four days later. A fourth CT scan showed definite aggravation. The second operation showed diffuse necrotizing pancreatitis with leakage from the jejunostomy; necrosectomy (40 g) was performed again. The patient died 16 hours later despite intensive reanimation. Relatives refused the autopsy. Serum amylase and lipase values remained normal during the entire course.

A 55-year-old woman with alcoholic cirrhosis and cardiomyopathy was hospitalized for upper abdominal pain of two days duration. On admission amylase was 85 IU/L, lipase was 310 U/L, urinary amylase was 62 IU/L, and Ranson's score was 2. CT scan showed ascites, a slightly enlarged pancreas, and edema within the mesenteric root and both Gerota fascias. Percutaneous peritoneal lavage was started. Peritoneal determinations of amylase and lipase in the first liter of lavage were 350 IU/L and 700 U/L, respectively. Multiple organ failure developed and she was transferred to the intensive care unit. A second CT scan (day 11) showed a larger pancreas and numerous phlegmons within its head. The third CT scan at 1 month revealed unaltered EPSs but a pseudocyst in the head of the pancreas. The patient was deemed to be inoperable and died on the 44th day of hospitalization. Autopsy disclosed extensive hemorrhagic and necrotizing pancreatitis.

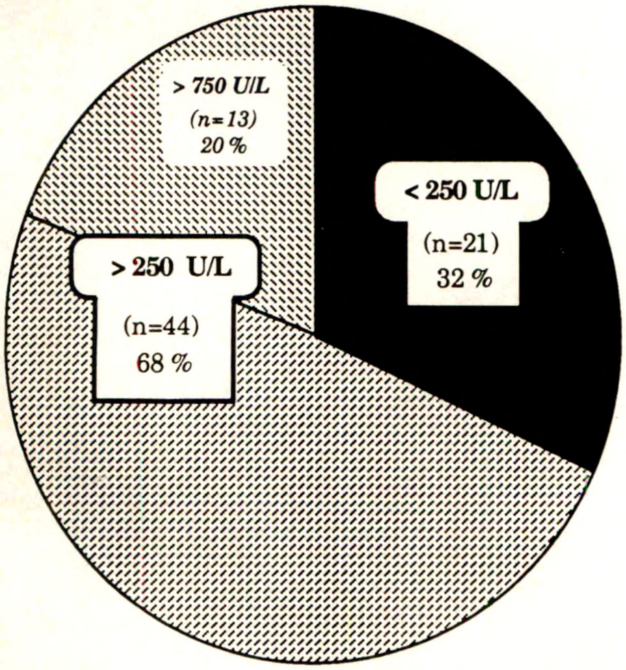


FIG. 3. Serum lipase concentrations at admission in 65 cases of normoamylasemic acute pancreatitis. (Reference values for serum lipase: 0 to 250 UK.)

A 62-year-old man with some degree of renal insufficiency due to polycystic kidney disease underwent a subtotal gastrectomy for gastric cancer. Four days after operation he became comatous and developed respiratory failure. No anastomotic leakage was seen on the contrast media meal. Serial determinations of serum amylase and lipase, on postoperative days 1, 3 to 9, and 14 were inferior to 60 IU/L and 400 U/L, respectively. The patient died on day 15 with multiple organ failure. Autopsy revealed diffuse hemorrhagic pancreatitis with retroperitoneal necrosis.

Serum amylase variations during the clinical course. In normoamylasemic pancreatitis, serum amylase rose at least once beyond normal values in 27 of the 67 cases (40%) and exceeded 500 IU/L in 7 (10%). Variations of serum amylase during hospital course were assessed by computing standard deviations (SD) that ran from 20 to 710 IU/L and did not appear to be related to severity of the clinical course (Kruskal-Wallis test). In the group of AP with hyperamylasemia, outcome was not related to initial amylase (ranging from 165 to 4000 IU/L, median 740 IU/L), nor to its variations.

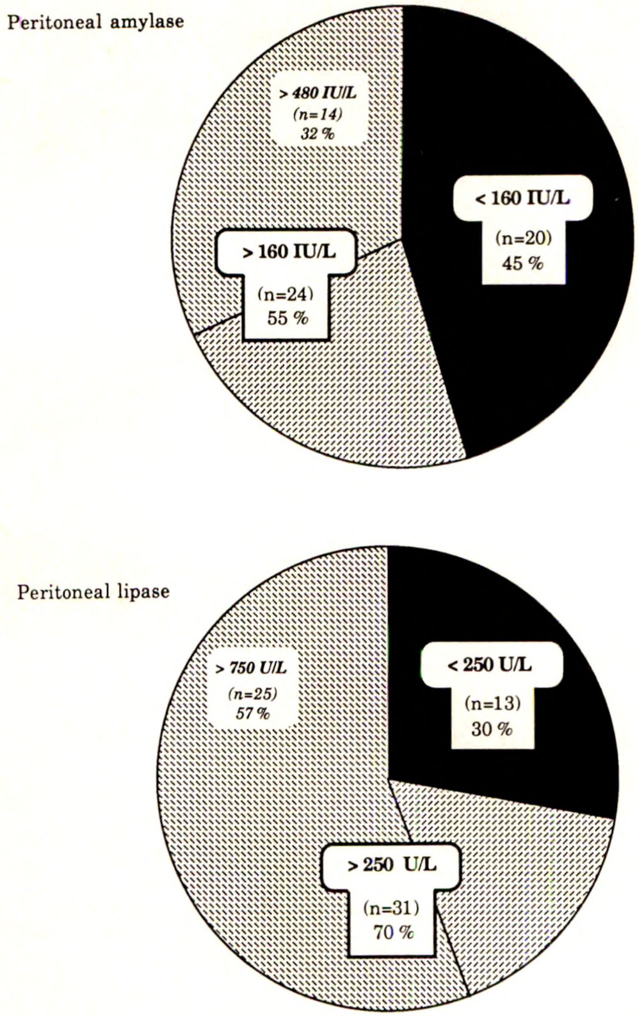
Other Enzymatic Determinations in AP with Normal Serum Amylase

Serum lipase was determined within 24 hours of hospitalization or of onset in cases of postoperative pancreatitis. As shown in Figure 3, two thirds of the cases had increased serum lipase, 20% of them exceeding three times the upper normal value. Urinary amylase was measured in 37 and was found to be normal in 27 (73%), exceeding twice the normal upper value in only one case.

Amylase and lipase were determined in the first liter of dialysis in 44 attacks within the initial 36 hours of hospitalization (Fig. 4). No amylase values higher than 600 IU/L were noted. Although peritoneal lipase was more frequently elevated than peritoneal amylase, this difference was not significant ($p = 0.2$; Mann-Whitney test). On the other hand, 12 attacks (27%) had no increase in serum and peritoneal concentrations for both enzymes. Ten of these 12 attacks had no increase in serum amylase during the whole clinical course. Diagnostic sensitivities achieved by serum and peritoneal enzyme determinations are presented in Table 2.

Discussion

This study was triggered by the observation of rare cases of unsuspected pancreatitis discovered at laparotomy or autopsy and which had presented as acute abdomens. The purpose of this report is to define the true incidence of AP by the systematic use of CT scan performed within 36 hours of admission in any case of abdominal pain suggestive of a pancreatic origin, regardless of amylase



FIGS. 4A and B. (A) Peritoneal amylase and (B) lipase concentrations in 44 cases of normoamylasemic acute pancreatitis.

TABLE 2. *Diagnostic Sensitivity of Amylase and Lipase in Acute Pancreatitis*

	False-Negative Results	Total	Sensitivity (%)
Serum amylase alone	67	352	81
Serum amylase and lipase	21	350*	94
Serum amylase and peritoneal amylase and lipase	13	329†	96
Serum and peritoneal amylase and lipase	12	329†	96

* Two cases of normoamylasemic AP had no serum lipase determination and were subtracted from the total.

† Twenty-three cases of normoamylasemic AP had no peritoneal enzyme determination and were subtracted from the total.

values obtained on admission (*i.e.*, even when this enzyme was within normal limits). Although expensive, CT scan appears to be the gold standard in AP, as shown by the many authors who use it.[1,6-8] A recent report from this institution covering 177 cases of AP showed CT to have a 100% specificity (no false-positive findings) and a 92% sensitivity.[7] The second objective was to see if normoamylasemic AP behaved differently than classical hyperamylasemic pancreatitis. Finally, when available, serum lipase and peritoneal amylase and lipase determinations were evaluated to see if they could unmask normoamylasemic AP.

In the present report, 67 of 352 cases of AP were admitted with normal serum amylase levels. This represents a 19% incidence, a figure significantly higher than commonly admitted.[1-3,5,6,17,18] In a series of 68 episodes of alcoholic pancreatitis, Spechler et al.[4] reported a surprisingly high 32% incidence of AP with normoamylasemia, despite questionable CT imaging criteria and despite the fact that CT confirmation was obtained in only two thirds of their cases.[19] Most, if not all, authors parallel AP with hyperamylasemia with threshold diagnostic levels of serum amylase generally arbitrarily chosen and ranging from one to nine times the upper normal value, the higher factors intended to eliminate more false-positive results.[1-8,11,15,17,18,20]

Another source of confusion resides in the facts that more than 200 techniques of amylase determination have been described since Magendie's inaugural protocol in 1846 and that no international reference method has yet been adopted.[20,21]

Why Do Normoamylasemic APs Exist?

There are many reasons to reconcile AP with normal amylasemia on admission. This enzyme is believed to rise within 24 hours after onset of the disease and return to normal within five days.[1,20-22] In this series duration of symptoms before admission was longer in the group of normoamylasemic patients, the difference being greater in biliary than alcoholic pancreatitis. Studying serum amylase profiles, Hiatt et al.[18] showed that the decrease in amylase occurred significantly faster in biliary than in alcoholic pancreatitis. In the present survey, some patients might well have been admitted after amylase had returned to normal. This seems particularly true for mild biliary pancreatitis resulting from transient papillary stone obstruction.

Another possible explanation is that in relapsing and/or alcoholic pancreatitis, deteriorated parenchyma is no longer able to produce sufficient amounts of enzymes.[4,9,10,22-24] Even though the distinction between relapsing AP and exacerbation of chronic pancreatitis is sometimes impossible (in fact, absent from recent international classifications of pancreatitis[9,10]), the 21 attacks with a story of previous similar episodes and alcoholic abuse in the present series did not appear to suffer from chronic pancreatitis because none of them showed pancreatic duct dilatation, calcifications on CT scan, or signs of pancreatic exocrine insufficiency.

Some authors have postulated that severe necrotizing pancreatitis may yield falsely reassuring serum amylase levels, as was the case in one patient in this series who died with massive pancreatic destruction after subtotal gastrectomy. However this was not the rule in our study because the two other fatal cases with normal amylase had suffered from relatively mild disease in terms of Ranson's score and CT findings on admission; associated conditions such as advanced age, liver cirrhosis and cardiopathy certainly played an important part. In fact, AP did not appear to be more severe in the normoamylasemic group: the clinical course was deemed difficult in 30% of cases compared to 40% when amylase was elevated.

Finally, in those rare cases of lactescent plasma, false-negative amylase results were circumvented by serial dilution techniques.[25]

Do Normoamylasemic APs Behave Differently?

Initial serum amylase is usually believed to bear no prognostic significance,[1,20,22,23,26] although cases of severe AP without hyperamylasemia have been reported.[2–6,20,26,27] In the experience of Albo et al.,[27] for instance, one third of their very ill patients with hemorrhagic pancreatitis had normal amylasemia, suggesting that amylase levels could be inversely related to the severity of the disease. In the present series, when considering CT scan, Ranson's score and clinical course, AP did not behave differently in terms of statistical significance whether amylase on admission was normal or elevated, although there was a tendency for normoamylasemic attacks to follow milder courses. It is likely that most benign normoamylasemic attacks would have been misdiagnosed without the use of CT scan. On the other hand, independent of initial amylasemia, variability of serial serum amylase during the clinical course as assessed by standard deviations was not related to the severity of the disease, a finding previously reported.[23]

Can more reliable tests be advocated to detect or confirm AP when serum amylase is not elevated or when CT scan is not available, as is often the case in smaller hospitals? Although quite accurate, immunoreactive trypsin, elastase-1, phospholipase A_2, carboxylic ester hydrolase, and carboxypeptidase determinations are seldom resorted to in the emergency setting due to their complexity.[1,28–31] Likewise electrophoretic determinations of amylase isoenzymes and the amylase/creatinine clearance ratio, however promising in enhancing the diagnostic specificity of amylase, appear to be of limited value when serum amylase is within the normal range.[1,29–35] Urinary amylase, considered by some as more sensitive than serum amylase in detecting AP,[35] was equally disappointing in our experience because it was significantly elevated in only one of 37 instances of normoamylasemic AP.

Assaying of lipase, which rises after amylase and remains elevated longer, had not gained wide acceptance.[1,29,31,35,36] And yet, in the present series, 44 of 65 cases of normoamylasemic AP (68%) had elevated lipasemia, thus increasing diagnostic sensitivity from 81% when serum amylase alone is used to 94% when both enzymes are considered. Lipase is also believed to rise more than amylase in cases of alcoholic pancreatitis.[34–36] The combined assaying of colipase might enhance the accuracy of lipase determinations.[36]

Little additional help in diagnosis was obtained when considering peritoneal determinations of both enzymes (from 94% to 96%). Strangely enough peritoneal amylase hyperconcentrations were not necessarily associated with elevated serum levels as if they were too low (less than 600 IU/L) to produce hyperamylasemia.[38] Peritoneal absorption is probably not the most important mechanism involved in increasing plasma levels. Recently increased plasma amylase was found to result first from direct venous drainage followed by lymphatic drainage *via* the thoracic duct.[39] In our series peritoneal and serum concentrations were better correlated for lipase.

In conclusion these results do not minimize the diagnostic value of serum amylase, which remains the simplest and most readily available test in AP.[1,7,20–22,28–31] However normal serum amylase levels on admission should not dismiss the diagnosis of AP, and future classifications of pancreatitis mention the fact that hyperamylasemia is not a necessary condition for the diagnosis of AP. Approximately two thirds of cases with normal amylasemia were properly identified by lipase determinations. CT scan should be used in case of doubtful or negative enzymatic results.[7,31] Finally AP does not appear to behave differently if serum amylase is normal or elevated and should, therefore, be submitted to similar therapeutic regimens in both conditions.

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Strictureplasty in Crohn's Disease

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Fifty patients with fibrotic small bowel strictures secondary to long-standing Crohn's disease underwent a total of 225 strictureplasties during the period from June 1984 to July 1988. Forty-two patients (84%) presented with obstructive symptoms. Patients had a 1- to 30-year history of Crohn's disease (mean, 14 years). Sixty-two per cent of patients were taking steroids at the time of admission, and 70% had had previous small bowel resections. All patients had one or more areas of small bowel affected with a fibrotic stricture and partial obstruction. Short strictures were treated by Heinecke-Mikulicz strictureplasties, and longer strictures by Finney side-to-side strictureplasties. In 30 patients (60%), 6- to 65-cm segments of small bowel were also resected due to acute inflammation with phlegmon or fistulae. Patients were discharged from the hospital 5 to 20 days after operation (mean, 10 days). After operation all patients with obstructive symptoms reported relief of symptoms and weight gain. Steroid doses could be tapered and nutritional parameters, such as total lymphocyte count, and serum albumin improved. Strictureplasty had 0% mortality and 16% morbidity rates. Complications included 3 enterocutaneous fistulae, 2 intra-abdominal abscesses, 2 hemorrhages requiring transfusion, 1 prolonged postoperative ileus that could be treated conservatively in 2 patients, and 1 restricture of a strictureplasty. Patients were followed for 1 to 40 months after operation (mean, 8 months). Resection of small bowel disease, especially that associated with perforation, is usually required in Crohn's disease. However, strictureplasty minimizes the need for bowel resection in patients with short fibrotic strictures resulting in recurrent small bowel obstruction.

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DURING THE PAST 40 years, the surgical philosophy regarding the optimal treatment of Crohn's disease has undergone many changes. In 1954 Garlock and Crohn reported a fairly high (16.4%) mortality rate after excisional surgery for Crohn's disease.[1] This resulted in frequent use of bypass procedures rather than resection during the 1950s and 1960s. Since that time the following factors have resulted in a shift in favor of resection: (1) a higher incidence of local septic complications with bypass because the diseased bowel was left in place;[2] (2) higher recurrence rates after bypass procedures than compared with resection (94% after bypass in continuity *vs.* 82% after exclusion bypass, and 64% following resection);[3] (3) the risk of carcinoma developing in bypassed small bowel;[4] (4) a decrease in surgical mortality rates after resection due to improved perioperative care.

With the subsequent return to excisional surgery as the treatment of choice for Crohn's disease, there was much controversy regarding the extent of resection (*i.e.*, disease-free margins of resection). This is particularly important because many of these patients require additional surgery. A study in which patients were followed for more than 10 years showed that 53% of patients with ileocolic Crohn's disease who had undergone surgery developed at least one recurrence requiring further surgical intervention.[5] In such patients radical small bowel resection of all macroscopically diseased segments could result in vitamin B 12 and folate deficiency, anemia, chronic malnutrition, and in some cases, short bowel syndrome severe enough to require home hyperalimentation.

Wolff et al.[6] were able to demonstrate higher recurrence rates in Crohn's disease patients with microscopic disease at the margins of resection, while others have demonstrated no difference in actuarial recurrence rates in patients with and without microscopic disease at the margins of resection.[7-9] In addition several studies have shown that microscopic changes of Crohn's disease may be present in macroscopically normal-appearing bowel.[10,11] Presently most surgeons realize that Crohn's disease is a panintestinal phenomenon and cannot be cured by ex-

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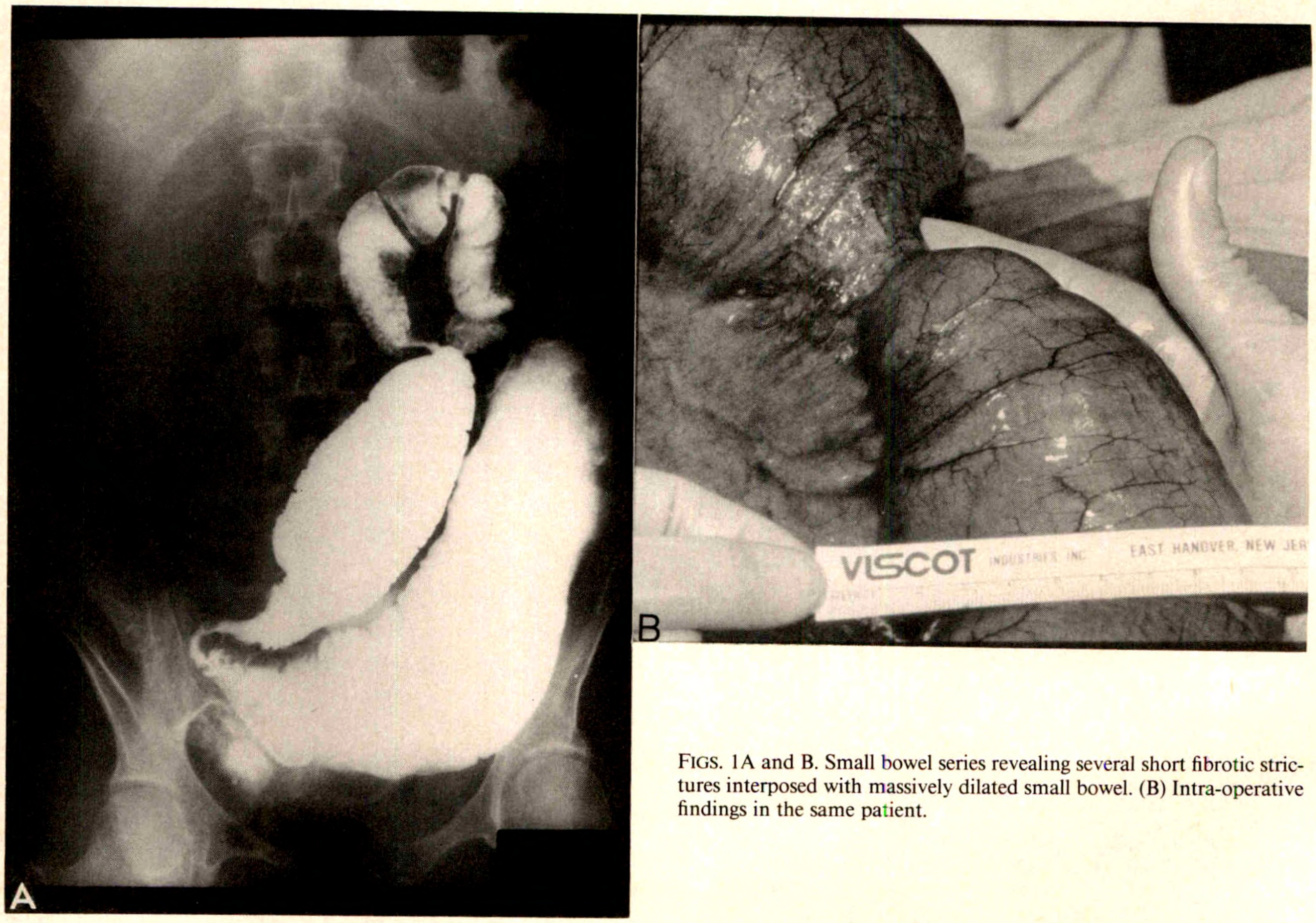
cision alone. Increasingly surgeons are becoming more conservative with respect to surgery for Crohn's disease, with the following principles of management:[12,13] (1) treat the specific complication, (2) make the operation as safe as possible, keeping the number of anastomoses to a minimum, (3) conserve bowel and avoid unnecessary bowel resection, (4) do not perform anastomoses when gross sepsis is present, and (5) do not leave strictured or stenosed bowel segments behind.

Approximately 12% to 35% of Crohn's patients will have skip lesions.[14] These may take the form of short areas of thickened mesentery and bowel, with fat wrapping, and serositis, or may be manifest as multiple, short, fibrotic strictures (Fig. 1). As partial obstruction in these strictured areas persists, secondary increases in intraluminal pressure may force enteric contents into fissures or ulcers in the mucosa, resulting in further inflammation of the bowel wall and progressive fibrosis. When such strictures are located some distance apart from each other, resection would involve multiple anastomoses and loss of large segments of small bowel.

Patients with diffuse Crohn's jejunoileitis pose a special problem. In Cooke and Swan's series, 13 of 18 patients required surgery for recurrent intestinal obstruction, with more than one half of these requiring reoperation.[15] It is unclear whether this is a separate entity, or a final stage of the disease. Marshak and Wolff[16] described the radiologic progression of Crohn's disease from the nonstenotic form, to disease with multiple cicatricial strictures and long segments of stenosed bowel. In contrast Prantera[17] believes that patients with strictures represent a different subset of Crohn's patients rather than a phase of evolution. He reviewed radiologic findings in 64 patients with Crohn's disease who had not undergone previous resection. Twenty-five patients had a stricture at the time of presentation and the duration of their symptoms was no longer than that of patients without strictures.

The concept of increasing luminal diameter without resection, in the manner of a pyloroplasty, was reportedly first performed in a patient with Crohn's disease in 1961.[13] Subsequently the same technique has been used in India to successfully treat intestinal strictures secondary to tuberculosis.[18] In 1979 Lee[19] began routinely using this technique to treat select Crohn's patients with multiple, short, fibrotic strictures of the small bowel. Here we report our experience with strictureplasty in Crohn's disease.



FIGS. 1A and B. Small bowel series revealing several short fibrotic strictures interposed with massively dilated small bowel. (B) Intra-operative findings in the same patient.

Materials and Methods

During the period from June 1984 to July 1988, 225 strictureplasties were performed for small bowel Crohn's disease in 50 patients. Patient data is listed in Table 1. The indication for surgery was obstruction in 42 patients, and perforation/obstruction in four patients. In four patients asymptomatic strictures were incidental findings at laparotomy for other reasons (cholecystectomy, completion proctectomy, stoma revision, and exploration for an ileal lesion seen on small bowel series). One hundred ninety-nine short strictures were treated by Heinecke-Mikulicz strictureplasties, and 26 longer strictures (up to 15 cm) were treated by side-to-side Finney strictureplasties (Fig. 2). All Heinecke-Mikulicz strictureplasties were performed using one-layer interrupted vicryl sutures. The Finney strictureplasties were either hand sewn, or constructed using a GIA stapler. Thirty patients (60%) also underwent resection of 6- to 65-cm segments of small bowel during the same operation. Indications for resection in these cases included acute inflammation, perforation, fistulae, long strictures (greater than 30 cm), and the presence of multiple strictures very close to each other. Twenty patients underwent strictureplasty alone without resection.

At the time of surgery, the antimesenteric margin of the involved small bowel was relatively free of disease, *i.e.*, not as indurated and thinner than the mesenteric margin. On opening the bowel in the strictured area, a Crohn's ulcer was frequently present on the mesenteric margin. Biopsies of this ulcer were performed in 32% of patients, and 63% of these were positive for active Crohn's disease on histologic examination.

The mean postoperative hospital stay was 10 days (range, 5 to 20 days). All patients with obstructive symptoms reported relief after operation. Ten postoperative complications secondary to strictureplasty occurred in eight patients (16%). Complications included enterocutaneous fistulae in three patients, which required reoperation in two patients, and treatment with hyperalimentation in another patient. Intra-abdominal abscess occurred in two patients. In one patient (who underwent concomitant bougie dilatation of a long segment), the abscess was treated with parenteral antibiotics alone, while in the other patient CT-guided drainage was required. Two patients had hemorrhage requiring transfusion; in one of these, four units of packed red cells were needed in a patient who subsequently developed an abscess. The other patient required transfusion of eight units of blood and three units of plasma, as well as systemic Pitressin (Parke-Davis, Morris Plains, NJ) for bleeding possibly originating from an ileocolic anastomosis by angiography. Two patients had small bowel obstruction treated conservatively but requiring hospital admission. In another patient restricture of a previous strictureplasty site occurred 17 months after operation.

TABLE 1. *Patient Data*

Mean age	37 years (range, 15–71 years)
Mean duration CD	14 years (range, 1–30 years)
Previous SB resection(s)	35 patients (70%)
Short bowel syndrome	12 patients (24%)
Prednisone	31 patients (62%; mean dose, 22 mg/d; range, 2.5–60 mg/d)
Preoperative weight loss	22/50 patients (44%; mean, 8 kg)

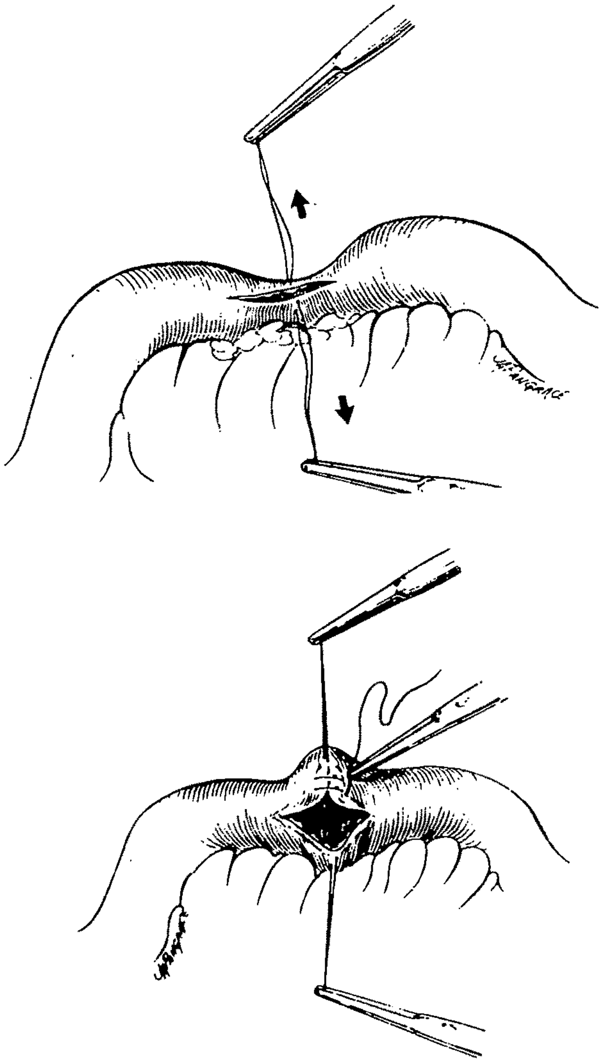


FIG. 2. Heinecke-Mikulicz strictureplasty.

Patients were followed after operation for 1 to 40 months (mean, 8.3 months). Nutritional parameters such as weight, serum albumin, and total lymphocyte count improved, with a mean weight gain of 5 kg, a mean rise in serum albumin of 0.8 g/dL, and an increase in total lymphocyte count by 440. During that time 11 laparotomies were performed for complications of Crohn's disease, including new stricture formation in four patients.

These new strictures were also treated by strictureplasty. Restricture at one strictureplasty site was observed at relaparotomy in one patient as described above. All other strictureplasty sites showed no evidence of stricture. In most patients it was even difficult to identify previous strictureplasty sites.

Discussion

Since Lee's report on minimal surgery for Crohn's disease, several investigators have reported the use of strictureplasty in Crohn's disease[13,20-24] (Table 2). Our complication rate is comparable to that of other series (Table 3). Strictureplasty is not associated with morbidity rate higher than that seen with resection. Despite the presence of gross disease, the bowel accepts and retains suture material remarkably well. At relaparotomy, strictureplasty sites are often hard to identify, supporting the concept that increased intraluminal pressure, secondary to the obstruction at these areas, may be responsible for progression of the inflammation and fibrosis seen if strictures are not treated.

The importance of strictureplasty in conserving bowel is evident when one considers that 15 of 127 patients (12%) undergoing strictureplasty developed new strictures that required further surgical intervention in the reported literature.

Endoscopic or operative dilatation of strictures is another bowel-sparing treatment for strictures. Alexander-Williams reported restenosis in two of five patients who had undergone dilatation of small bowel strictures over a follow-up period of 5 months to more than 2 years.[25]

The basic issue in performing strictureplasty is patient selection. Strictureplasty is not intended to replace excision, but rather augment the existing surgical armamentarium. Strictureplasty is indicated to treat long-standing, short fibrotic strictures secondary to Crohn's disease, and for those patients with symptomatic strictures after previous small bowel resection. Strictureplasty may be performed if there is no acute inflammation or phlegmon at the strictured area. On small bowel series, dilated loops of small bowel are interposed between tight, short strictures. Strictureplasty is suitable for patients with extensive Crohn's jejunoileitis with symptomatic strictures, and in patients in whom resection of strictures would result in loss of large segments of normal bowel. If the patient is severely malnourished, preoperative intravenous hyperalimentation is indicated. Strictureplasty may also be used to treat anastomotic strictures in the absence of gross disease (*i.e.*, ileocolic anastomotic stricture).

TABLE 2. *Strictureplasty 1979–1988*

Author	Number of Patients	Number of SXPL
Present series	50	225
Alexander-Williams (Birmingham)	57	146
Kendall (St. Marks)	7	45
Whelan (Toronto)	3	15
Pace (Long Island Jewish)	1	8
Lee (Oxford)	9	9
Total	127	448

SXPL, strictureplasty.

TABLE 3. *Strictureplasty-Related Complications (Literature Review 1979–1988, n = 127)*

Complication	Number of Patients	(%)
Mortality	0	0
Prolonged ileus	3	2
Hemorrhage requiring transfusion	2	2
Small bowel carcinoma	1	1
Fistula/abscess/leak	11	9
Restricture of sxpl. site	3	2
Total	20	16
Subsequent new strictures at other sites	15	12

SXPL, strictureplasty.

Strictureplasty, however, should not be performed in the presence of phlegmonous inflammation, perforation, or peri-intestinal abscess. Further contraindications are multiple strictures in a very short segment or strictures in close proximity to a site chosen for resection. The ability to perform a strictureplasty is limited by the pliability of the bowel wall. It should be avoided in bowel that is rigid and not easily bent back on itself. In addition, with very long strictures, a Finney strictureplasty could result in construction of a very long blind limb with questionable absorptive capacity. Although strictureplasty has been performed for colonic strictures,[26] we have not used it in this manner.

Strictureplasty can be easily and safely performed in Crohn's disease patients who are on steroids and who have recurrent small bowel obstructions secondary to multiple fibrotic strictures. Although strictureplasty is often performed in bowel with signs of active Crohn's disease, these sites tend to heal. Relaparotomy in these patients has shown that dilatation of adjacent loops of bowel and fibrotic changes of the strictured area tend to resolve with time. Restricture occurred in only one of the strictureplasties in this series. Strictureplasty has a morbidity rate comparable to that of resection and, with proper patient selection, can be used safely and effectively to increase luminal diameter in Crohn's patients with recurrent small bowel obstruction secondary to short fibrotic strictures.

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Nonoperative Management of Adult Blunt Splenic Trauma

Criteria for Successful Outcome

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Nonoperative management of blunt splenic trauma in adults is controversial despite numerous reports advocating this mode of therapy. Blunt splenic trauma is frequently managed without operation at our institution and, to define criteria that may predict a successful outcome, a retrospective review (1980 to 1988) of all adult splenic injuries was undertaken. Splenic injuries were documented by scintillation studies, CAT scanning, or at laparotomy. Sixty of 252 (24%) splenic injuries were initially treated without operation, which included bed rest, ICU monitoring, frequent physical exams, nasogastric tube, serial hematocrits, and follow-up splenic imaging. Five patients (5 of 60) failed nonoperative management and required interval laparotomy. Reasons for failure included blood loss greater than four units, enlarging splenic defect, or increasing peritoneal signs. Parameters predicting a successful outcome were localized trauma to the left flank or abdomen, hemodynamic stability, transfusion requirements less than four units, rapid return of GI function, age less than 60 years, and early resolution of splenic defects on imaging studies. No morbidity or deaths resulted from delayed operative intervention. In carefully selected adult patients, blunt splenic trauma may be successfully managed without operation.

THE MANAGEMENT OF SPLENIC trauma has changed dramatically in the past decade. Until recently total splenectomy was considered the only treatment for the patient with an injured spleen. This procedure eliminated the risk of postoperative splenic hemorrhage and was believed to pose no further detriment to the patient. Recent studies have shown, however, that asplenic patients are at an increased risk from a number of postoperative complications such as pulmonary and wound infections, thromboembolic sequelae, overwhelming postsplenectomy sepsis, and possibly fatal coronary artery disease.[1-4] The risk for fatal postsplenectomy sepsis, initially described in children and patients with hematologic disorders, is now recognized to include the adult patient as well. Postsplenectomy sepsis may occur in the absence of underlying disease and may occur several years after splenectomy.[5] Within the past decade techniques of splenic preservation (including segmental resection, splenorrhaphy, autotransplantation of splenic fragments, and nonoperative management) have been introduced to avoid these potential problems.

The concept of selective, nonoperative management of blunt splenic injuries is now widely practiced among pediatric surgeons.[6,7] Most surgeons, however, have been reluctant to consider this approach in adults for fear of such complications as delayed splenic rupture, traumatic splenic cyst formation, failure to identify other serious intra-abdominal injuries, and the development of posttraumatic splenosis. Several investigators have recently examined the role of nonoperative therapy for splenic injuries in adults (Table 1). These reports suggest that a high success rate for nonoperative treatment may be achieved if criteria are established that can help predict which patients are suitable candidates. In addition guidelines for deciding when a patient has failed nonoperative therapy have yet to be established. To better define such criteria, we have retrospectively reviewed our 8-year experience with operative and nonoperative management of blunt splenic trauma in adults.

Patients and Methods

Two hundred fifty-two adult patients (16 years or older) were treated at the Yale New-Haven Hospital with documented blunt splenic injuries during the 8-year interval from 1980 to 1988. Patients with penetrating abdominal trauma and splenic injuries were not considered as candidates for nonoperative management. Sixty patients with documented splenic injuries after blunt trauma initially treated without operation are the subject of this report. The diagnosis of splenic injury was suggested by the mechanism of injury and/or the physical examination.

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TABLE 1. *Nonoperative Management of Splenic Injuries in Adults*

Source	Year	Number of Patients	Delayed Splenectomy (%)	Percentage of all Splenic Injuries (%)
Strauch	1979	2	0	N/A
Lutzker	1981	9	0	N/A
Hebeler	1982	32	1 (4)	19
Morgenstern	1983	17	0	31
Zucker	1984	14	1 (7)	29
Johnson	1984	11	3 (27)	18
Malangoni	1984	10	7 (70)	13
Johnson	1986	11	3 (27)	18
Andersson	1986	13	0	25
Moss	1987	7	2 (29)	23
Wiebke	1987	10	3 (30)	N/A
Wiig	1987	32	0	33
Nallathambi	1988	10	7 (70)	21
Resciniti	1988	27	10 (37)	31
Buntain	1988	10	0	28

N/A, information not available.

TABLE 2. *Mechanism of Injury (Nonoperative Management)*

Mechanism	Number	Per Cent
Motor vehicle	20	33
Fall	13	22
Assault	9	15
Contact sports	8	13
Motorcycle	5	8
Auto–pedestrian	3	5
Bicycle	2	3

Injuries were subsequently confirmed by liver–spleen scintillation scanning, computed tomography (CT), or laparotomy.

The management protocol for patients with suspected splenic trauma was as follows: (1) patients with hemodynamic instability or who had diffuse peritoneal findings underwent emergency laparotomy; (2) patients suspected of sustaining other intra-abdominal injuries, who had equivocal physical findings, or altered mental status, underwent immediate peritoneal lavage; and (3) patients who were stable and had a high clinical suspicion of isolated splenic injury underwent immediate liver–spleen scintillation studies or CT scanning. The ultimate decision regarding the method of treatment for each patient was made by the attending surgeon.

After the decision to treat a patient without operation was made, absolute bed rest was instituted along with nasogastric tube decompression, cardiac monitoring, blood pressure and urine output, frequent physical examinations, serial hematocrits, and follow-up splenic imaging studies. Blood was transfused as necessary to maintain a hematocrit level greater than 30%. Generally transfusion requirements of more than four units of blood, persistent leukocytosis, increasing peritoneal irritation, hemodynamic instability, or an enlarging splenic defect on imaging studies were considered as indications for surgical intervention.

Patients were instructed to refrain from participating in vigorous exercise and contact sports for 2 to 3 months after splenic trauma. Follow-up scintillation scans were obtained 3 months after discharge to assess splenic healing.

Results

The age range of the 252 patients was 16 to 74 years, with a mean age of 34.5 years. Sixty (24%) adult patients with documented blunt splenic trauma were initially treated without operation. Mechanisms of injury are shown in Table 2. More than one half (61%) of the patients who were treated without operation sustained a low-velocity deceleration injury or direct blow to the abdomen. The remaining patients were passengers in automobiles or motorcycles, or were pedestrians struck by vehicles. In 43 patients (17%) splenic preservation was accomplished with operative splenorrhaphy and the remaining 149 operated patients (59%) were managed by total splenectomy. None of these patients were treated with procedures involving angiographic splenic embolization, splenic autotransplantation, or splenic artery ligation alone. Splenic injuries were documented by liver–spleen scintillation scan in six patients (10%) and by CT scan in 54 patients (90%). The average age of patients treated without operation was 29.8 years (range, 16 to 79 years). The mean length of hospitalization was 10.4 days in the operative group and 8.5 days in the nonoperative group. In the nonoperative group, 36 patients had one or more nonfatal extra-abdominal injuries (Table 3).

Five patients (of 60) initially treated without operation underwent delayed splenectomy during the same hospitalization and were considered to be failures of nonoperative management. Four of these patients required more than four units of transfused blood. The mean transfusion requirement was 7 units (SEM ±1.4) of packed cells or whole blood in those patients who failed nonoperative management *versus* 3.1±1.1 units in those treated successfully without surgery. Three of five patients in the failure group were older than 60 years, and the mean age for this group was 54.4 years *versus* a mean age of 24.8 years for patients successfully treated without operation. Two patients underwent delayed splenectomy on the basis of increasing peritoneal signs on physical examination and one patient had a delayed splenectomy due to an enlarging splenic defect on CT scan. In all five patients who failed

TABLE 3. *Associated Injuries (Nonoperative Management)*

Injury	Number of Patients
Rib fracture	21
Long bone fracture	14
Major soft tissue injuries	9
Renal contusion	4
Pulmonary contusion	6
Pelvic fracture	2

a trial of nonoperative management, splenic injuries had occurred in motor vehicle crashes. Three of these patients had other extra-abdominal injuries such as long-bone fractures (3), pulmonary contusion (2), and pelvic fracture (3). The interval from injury to delayed operative intervention in the treatment failure group ranged from 6 to 94 hours. No other serious intra-abdominal injuries were found in those patients who underwent delayed laparotomy. One patient who underwent delayed splenectomy also had a renal contusion. There were no deaths in patients treated without operation or who underwent delayed splenectomy. The mean length of hospitalization for the treatment failure group was 11.2 days *versus* 8.2 days in those treated without surgery. The average length of follow-up in the nonoperative group was 26 months (range, 2 to 83 months). None of these patients have manifested any clinical evidence of splenic dysfunction (*i.e.*, sepsis) or rebleeding.

Discussion

During the past three decades our concept of the spleen as a vital organ has changed dramatically. Although in 1919 Morris and Bullock[8] reported experimental evidence that asplenic animals were at an increased risk of infection, these ideas were largely ignored and total splenectomy was considered the procedure of choice after injury. An awareness of the important immunologic function of the spleen was later suggested by King and Schumaker who, in 1952, reported five infants who developed fatal sepsis after splenectomy. Twenty years of controversy followed until the classic report of Singer in 1973, which reviewed the experience with postsplenectomy sepsis at the Texas Children's Hospital in Houston, as well as 23 other series from the literature. He found that the risk of developing postsplenectomy sepsis was increased, particularly in younger patients and in the presence of underlying hematologic disease.

It is well known that the spleen plays a major role in the clearance of particulate antigens and both humoral and cell-mediated immunity. The spleen is the site of production of opsonins, tuftsin, and properdin, which enhance phagocytosis, and is also the site of many fixed macrophages that remove particulate antigens from the bloodstream.[9,10] In addition B lymphocyte maturation and the production of both IgM and IgG occur in the spleen. It is also a site for maturation of T-helper, T-cytotoxic/suppressor cells, and natural killer cells.[12] Splenectomy has also been reported to be associated with a number of other perioperative complications such as pneumonia, intra-abdominal and wound sepsis, iatrogenic injury to the stomach and pancreas, thromboembolic complications, and even a potential delayed risk of ischemic heart disease.[2-4]

Coincident with the recognition of these problems, surgeons have developed a number of techniques for splenic conservation including partial resection, direct operative repair of splenic injuries (splenorrhaphy), autotransplantation of splenic fragments, as well as expectant, carefully monitored nonoperative management for isolated splenic injuries. Nonoperative therapy of selected cases of blunt splenic trauma was first advocated in 1968 by Upadhyaha and Simpson[12] who followed 12 children with suspected blunt splenic injuries. The lack of direct confirmation of these injuries, however, resulted in considerable criticism of their report. Shortly thereafter Werner and Boyle[14] described the reliability of the scintillation scan in the diagnosis of splenic injury. Since then an extensive experience with splenic injuries treated without operation has been reported by the Toronto group and this form of management has now become routine in many pediatric centers across North America.[15,16]

Nonoperative therapy in adults continues to meet with considerable resistance. Fears of possible delayed splenic rupture and hemorrhage, formation of post-traumatic splenic cysts, generalized splenosis, and failure to recognize other serious intra-abdominal injuries have led most surgeons to continue to support early operative intervention. Although numerous reports have appeared in the literature indicating that this form of therapy may be used with a high likelihood of success, failure rates as high as 70% have also been published (Table 1). This wide variation in results suggests that proper patient selection may be the most important parameter for successful outcome. Previous reports often have not documented criteria used to select those patients who may best benefit from nonoperative management. It is also important to establish guidelines for deciding early in the hospital course when a patient has failed such therapy.

Based on the excellent results obtained in the pediatric population, as well as earlier reports in adults, we developed a protocol for selecting adult patients with splenic injuries for nonoperative management. First only a minority of patients were suitable candidates for nonoperative therapy. Despite our interest in splenic preservation, only 24% of patients with blunt splenic trauma were included in this protocol. Other centers have reported similar results (Table 1). We also believe that patients with penetrating abdominal trauma are not suitable candidates for nonoperative therapy because of the high incidence of associated injuries.[17] Patients with altered mental status due to head trauma, alcohol or drug abuse, patients who were to undergo general anesthesia, or who were otherwise unable to participate in subsequent physical examinations (which are essential in the management of such patients) were also not considered candidates for nonoperative management. Patients suspected of sustaining other intra-abdominal injuries were also excluded from this protocol. Although hemodynamic stability was an important criteria for choosing nonoperative management, patients with brief episodes of mild hypotension that responded rapidly to fluid challenges generally were not excluded.

It should be emphasized that nonoperative management did not imply a lack of therapy or care. Once the patient was deemed a suitable candidate for nonoperative management, resuscitation with crystalloid or blood products was continued as needed. In addition all patients with confirmed splenic injuries (CT scan or scintillation study) not undergoing immediate operative intervention were confined to strict bed rest and monitored in an intensive care unit with nasogastric tube decompression (to prevent gastric distension and minimize the effects of post-traumatic ileus). In our experience changes in the physical exam have been the most reliable indicator of continued splenic hemorrhage. Follow-up imaging was performed three to five days after injury and if evidence of healing was present, nonoperative therapy was continued. Although earlier reports[18] emphasized the superiority of scintillation studies in the evaluation of the injured spleen, our recent experience indicates that with the current technology CT scanning is as accurate and sensitive as scintillation studies but also allows for the evaluation of other abdominal and extra-abdominal injuries. Patients were instructed to avoid physical straining or contact sports for a minimum of 3 months. Compliance and follow-up was good with nearly 75% of patients returning 3 months later for follow-up splenic imaging studies.

Although our number of management failures thus far has been small (5 of 60 patients), we have tried to establish early diagnostic parameters that indicate when nonoperative therapy may be failing. Mean blood transfusion requirements were twice as great (7.1±1.4 *versus* 3.1±1.1 units) in the treatment failure group as in patients treated successfully without surgery. Therefore we continue to advocate that patients requiring more than four units of packed red blood cells or whole blood should undergo laparotomy. Three of the five management failures were also older than 60 years and the mean age for this group was 54.4 years *versus* 24.8 years for those treated successfully. This finding of treatment failure in older patients has been reported previously.[19] Although our group and others have reported successful outcomes with nonoperative management in patients in their fifth, sixth, and even seventh decades, it is important to recognize that these patients may be more vulnerable to treatment failure. Two of these five patients were operated on due to recognition of increasing signs of peritoneal irritation alone. The fifth patient showed signs of increasing peritoneal irritation as well as an enlarging splenic defect on CT scan. At operation all three patients had actively bleeding splenic injuries. These results confirm our initial impression that the physical examination is a reliable indicator of continued intra-abdominal bleeding. In addition these three patients had prolonged post-traumatic ileus secondary to the hemoperitoneum. Although only one patient was found to have an enlarged defect on subsequent splenic imaging, we continue to obtain routine follow-up imaging studies 48 to 72 hours after admission to assess splenic bleeding.

By strict observance of these objective criteria, we have treated without operation many patients with splenic injuries. Our failure rate (8%) seems acceptably low and thus far has not resulted in serious additional morbidity or increased the number of deaths. All nonoperative management failures were detected during the initial hospitalization and there were no splenic complications occurring after discharge. The parameters that seemed to predict success of nonoperative therapy in our series were as follows: (1) hemodynamic stability after initial fluid challenge, (2) transfusion requirements of less than four units of blood, (3) age less than 50 years, (4) early resolution of splenic defects on imaging studies, (5) normal level of consciousness, and (6) rapid resolution of post-traumatic ileus. Identification of these parameters have enabled the surgeons in our institution to better predict those patients who are appropriate candidates for nonoperative management. In addition these criteria have guided our trauma service in determining much earlier when patients have failed this form of therapy and should undergo abdominal exploration.

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Alteration of Proliferation and Subtle Changes of Protein Synthesis in Autologous Transplanted Spleens

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In the case of massive splenic rupture, heterotopic autologous transplantation of splenic tissue into the omentum majus may be used to restore splenic function. Yet little is known about specific functions of the transplants compared to the normal spleen. The goal of this study was to get more information about immunologic functions and protein expression in splenic transplants. As an animal model we used the pig, whose splenic morphology and immunoarchitecture is similar to that of the human spleen. Histologic examination of transplants revealed structures that were comparable to normal spleens (consisting of red and white pulp and including germinal centers). Immunologic tests such as the hemolytic plaque assay and mitogen stimulation revealed that the number of plaque-forming cells was not changed significantly, but the stimulation index for T cells was drastically increased in the autotransplants. Electrophoresis and immunochemical methods showed differences in the protein patterns between both tissues. Several proteins were found to be produced only in the spleen, or were produced in much higher amounts in the spleen than in the splenic transplants. More information about these differences between spleen and splenic transplants is needed before we can recommend a general clinical application of autologous spleen transplantation.

SEPTIC COMPLICATIONS AFTER splenectomy and the assumed life-long risk for fatal sepsis have changed attitudes toward removing the spleen.[1,2] As a consequence several surgical approaches to repair a ruptured spleen and to preserve its function have been used.[3] One of these techniques is the autologous transplantation of the spleen, which seems to be the only alternative for splenic salvage after severe disruption of the organ. The main question, does splenic reimplantation provide a sufficient protection against postsplenectomy sepsis, is still unanswered.

Reimplantation of splenic tissue at various transplantation sites (such as the greater omentum or beneath the fascia of the abdominal muscles) results in the development of small splenic nodules that are histologically similar to a normal spleen. These neospleens are surrounded by a thin fibrous capsule, contain red and white pulp, including germinal centers, and their arteries indicate blood supply.[4-7]

Several experiments demonstrated the ability of the autotransplants to remove pitted erythrocytes and pneumococcal bacteremia.[8-11] The regenerated tissue also was shown to balance a prolonged IgM decrease in the serum, which occurs generally after splenectomy.[12]

In contrast to these data, which indicated no drastic differences between autotransplants and normal spleens, several investigations revealed alterations of the newly developed tissue. Measuring the blood flow using ^{99m}Tc-labelled albumin microspheres elicited a reduction of the perfusion rate in autotransplants compared to normal spleens.[13,14] Autotransplants also showed a different composition of lymphocyte subsets and an altered contribution of T suppressor cells to the circulating pool.[15-18] Furthermore the immunoarchitecture of regenerated splenic transplants is altered in the density of lymphocytes and the development of the marginal zone and the periarteriolar lymphatic sheath.[19-21] These differences in cell composition and immune architecture between the normal spleen and splenic transplants may influence functions of the transplants.

In contrast to most of the clinical and experimental reports concentrating on peripheral effects of the transplants (clearance of bacteremia, immune responses checked by serum antibodies, lymphocyte subpopulations in the blood, and so on) we focused mainly on two ap-

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proaches and tried to gather more information about functions of the transplant itself using the pig as an animal model. Functional assays such as measurement of the number of actively IgM producing B cells by direct hemolytic plaque assay and estimation of the proliferation rate induced by mitogen stimulation with T- and B-cell-specific mitogens were performed with autotransplant cells and compared to normal spleen cells. In addition the protein composition of both normal spleens and autotransplants was analyzed by SDS-polyacrylamide gelelectrophoresis (SDS-PAGE), two-dimensional gelelectrophoresis (2D-GE), and immunoblotting to search for a different expression of gene products in the cells of both tissues.

Materials and Methods

Animals and Operation

28 pigs (20 kg to 25 kg body weight, 8 weeks old) of the German Landrace strains were used for the experiments (autotransplantation group, n = 16; control group, n = 12).

Using general anesthesia (0.5 mg atropine sulfate, 0.08 mL/kg azaperone (Stresnil^R), 0.3 mL/kg Hypnodil^R), splenectomy was performed by a midline laparotomy. The spleen was decapsulated and minced into pieces of approximately 2 mm diameter. A defined quantity of this pulp (two thirds of splenic mass) was filled into the omentum majus, which was sutured tightly to avoid the penetration of splenic pulp into the abdominal cavity. Mitogen stimulation, and biochemical and immunochemical assays were performed 6 months after transplantation, and the hemolytic plaque assay was performed 12 months after transplantation.

Preparation of Cell Suspensions and Protein Extracts

The spleens or splenic autotransplants were gently teased with forceps in a Petri dish containing 10 mL Balanced Salt Solution (BSS).[22] The cell suspension was transferred to a graduated conical tube and the clumps of cells were allowed to settle for five minutes. The supernatant containing a homogenous cell suspension was transferred to another tube and the cells were washed three times in BSS (200 g for ten minutes).[22]

To extract proteins 100 mg of the pelleted cells were disrupted in 800 μL SDS-sample buffer for SDS-PAGE[23] or in 800 μL IEF-lysis buffer for 2D-GE.[24] After lysis of the cells, the suspension was centrifuged at 10,000 rpm for 15 minutes to obtain a clear protein extract without aggregates or particles.

Production of Antisera

One million spleen cells or autotransplant cells from pigs were injected into rabbits using an immunization schedule as described.[25] Four days after the last booster injection blood was taken from the ear vein and antiserum was won by centrifugation. The antisera were frozen and stored at −70 C.

Immunologic Assays

The direct hemolytic plaque assay was performed using the liquid matrix method between two slides.[22] Pigs (control group, n = 6; autotransplant group, n = 10) were immunized intravenously with 2.5 mL of 25% sheep red blood cells (SRBC) in phosphate buffered saline (PBS pH 7.2) plus 2.5 mL complete Freund's adjuvant (CFA).

Three days later the animals were killed and the spleens or splenic autotransplants were removed. A cell suspension was produced by mashing the tissue as described above. The cell number and viability were estimated in a hemacytometer chamber. Several dilutions of washed spleen cell suspensions and a constant amount of SRBC in Minimum Essential Medium Eagle (MEM Eagle, Sigma, Deisenhofen, FRG) with Earle's salts were pipetted together with rabbit serum as a complement source between two slides and incubated at 37 C. The number of plaque-forming cells/10^6 spleen cells (PFC) was determined after 3 hours. Because the implantation mode resulted in many separated splenic nodules in the omentum majus, up to three different transplants of one pig were used for the hemolytic plaque assays. The spleen of the control animals was also cut into pieces and each of them was used for one assay.

Mitogen stimulation (control group, n = 6; autotransplant group, n = 6) was performed with Concanavalin A (ConA, Sigma), Phytohemagglutinin (PHA, Sigma), Pokeweed mitogen (PWM, Sigma), and Lipopolysaccharide (LPS, Sigma) to measure the proliferation of both T and B cells.[22] A suspension (0.1 mL) containing 10^6 spleen cells was stimulated with 0 to 5 μg/mL ConA and PWM, 0 to 25 μg/mL LPS, and 0 to 50 μg/mL PHA (48 hours in MEM Eagle Dulbecco's modification). After this 48-hour culture period, 1.5×10^5 counts per minute (CPM) ^{3}H thymidine was added, and 24 hours later the cells were collected on filter discs with a Skatron cell harvester (Skatron, Lier, Norway). The filter discs were made transparent in scintillation vials containing a Beckman Ready Solve scintillation cocktail (Beckman Instruments, Palo Alto, CA) and radioactivity was measured in CPM by scintillation counting.

Controls were performed by treating the cells with mitomycin before stimulation with mitogens. All experiments were done in microtiter plates purchased from Nunc (Roskilde, Denmark), culture media, and mitogens obtained from Sigma.

Electrophoresis

Tissue of the spleens and autotransplants (100 mg to 200 mg) that were used for the mitogen assay were removed and prepared for electrophoresis (control group, n = 6; autotransplant group, n = 6). Parts of the spleens from the transplantation group were cut off before operation and this tissue was later compared to the homologous regenerated tissue.

SDS-PAGE was performed in a Dual-Slab-Gel-System (Protein Elpho-Cell, Biorad, Richmond, CA) using a gradient of 7.5% to 20% acrylamide and a discontinuous buffer system.[23]

Two-dimensional gelelectrophoresis was performed as described.[24] Characterization of the antigenic properties of proteins from spleens and autotransplants was done by immunoblotting against different antisera.[26] For that purpose the proteins separated by SDS-PAGE were transferred to a nitrocellulose sheet and antigen–antibody reaction was detected by an enzyme-linked antibody (goat-anti-rabbit peroxydase conjugate, Bio Rad).

Results

The mean weight of transplanted splenic tissue was 17.2 ± 5.9 g and resulted in a mean weight of 12.4 ± 7.6 g for the recovered tissue after 12 months (no increase in weight could be observed between 6 and 12 months).

Sixteen animals (control group, n = 6; autotransplant group, n = 10) were used for the estimation of the number of IgM-producing lymphocytes by the direct hemolytic plaque assay. Each spleen was cut into five pieces and the resulting parts were analyzed separately. In the autotransplant group the cells of three different splenic nodules (from one animal) were assayed. Both the control and the transplanted animals were immunized against SRBCs as described above. To clarify whether any spontaneous plaque formation occurs, cells from unimmunized control and transplanted animals were tested. Both groups elicited no plaque-forming cells, which demonstrated that the response of the immunized pigs was specific.

TABLE 1. *Mitogen Stimulation*

Mitogen	Concentration	Spleen	Autotransplant
Con A	0 μg/mL	137 ± 68	464 ± 268
	0.5 μg/mL	1665 ± 85	14930 ± 2900
	1 μg/mL	1422 ± 37	15968 ± 4774
	5 μg/mL	706 ± 167	9934 ± 5611
PHA	0 μg/mL	120 ± 20	335 ± 150
	1 μg/mL	529 ± 26	14009 ± 3020
	5 μg/mL	1431 ± 254	23762 ± 4778
	10 μg/mL	962 ± 330	26339 ± 7740
PWM	0 μg/mL	0	298 ± 107
	0.5 μg/mL	603 ± 4	15514 ± 4499
	1 μg/mL	684 ± 64	14006 ± 4775
	2.5 μg/mL	804 ± 12	15761 ± 3185
LPS	0 μg/mL	0	199 ± 113
	2 μg/mL	178 ± 42	439 ± 156
	5 μg/mL	186 ± 44	571 ± 65
	10 μg/mL	309 ± 65	661 ± 226

The data are expressed in delta CPM (the arithmetic mean of CPM from experimental [stimulated] cultures minus the mean of control [mitomycin-treated] cultures).

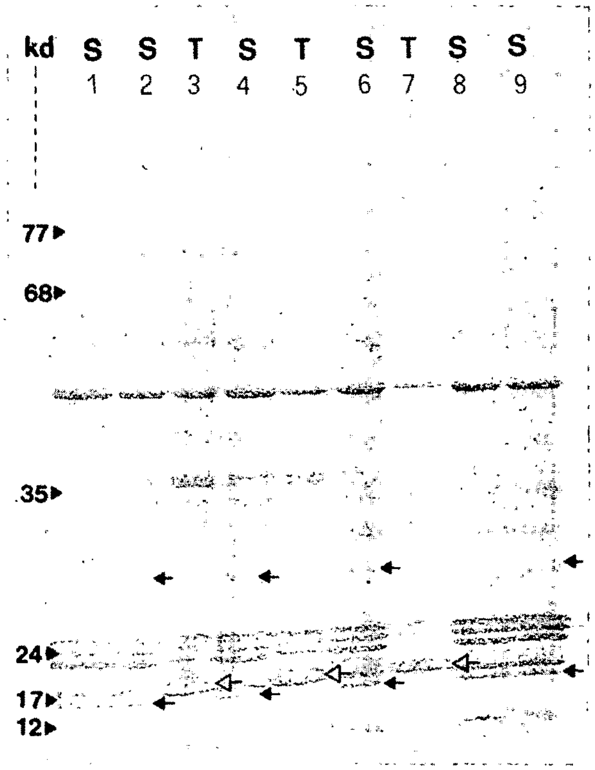


FIG. 1 SDS-PAGE of spleen cell extracts (S) and autotransplants (T). The molecular weight is shown on the left. Proteins expressed mainly in the spleen cells are indicated by closed arrows (molecular weight, 15 kd and 28 kd). The class of proteins that is enriched in the transplants is indicated by open arrows (molecular weight, 19 kd). Each lane represents the extract of one spleen or one autotransplant. The adjacent pairs of S and T (beginning with lanes 2 and 3) are homologous splenic and autotransplant extracts.

The number of PFC/10^6 spleen cells in the control group (30 probes) was 23.76 ± 16.78 and 18.84 ± 7.80 in the transplants (30 probes). Because the data were not normally distributed and the variances were different, the nonparametric U test was performed and revealed no significant difference of the means between both groups (significance level, 5%).

The results of the proliferation assay after treatment with various mitogens are shown in Table 1 (the relatively low stimulation values result from using only 10^5 cells and 1.5×10^5 CPM ^{3}H thymidine). The remarkable differences between the control and autotransplant groups indicate that quantitative and possibly qualitative alterations may have happened in the autotransplanted splenic tissue.

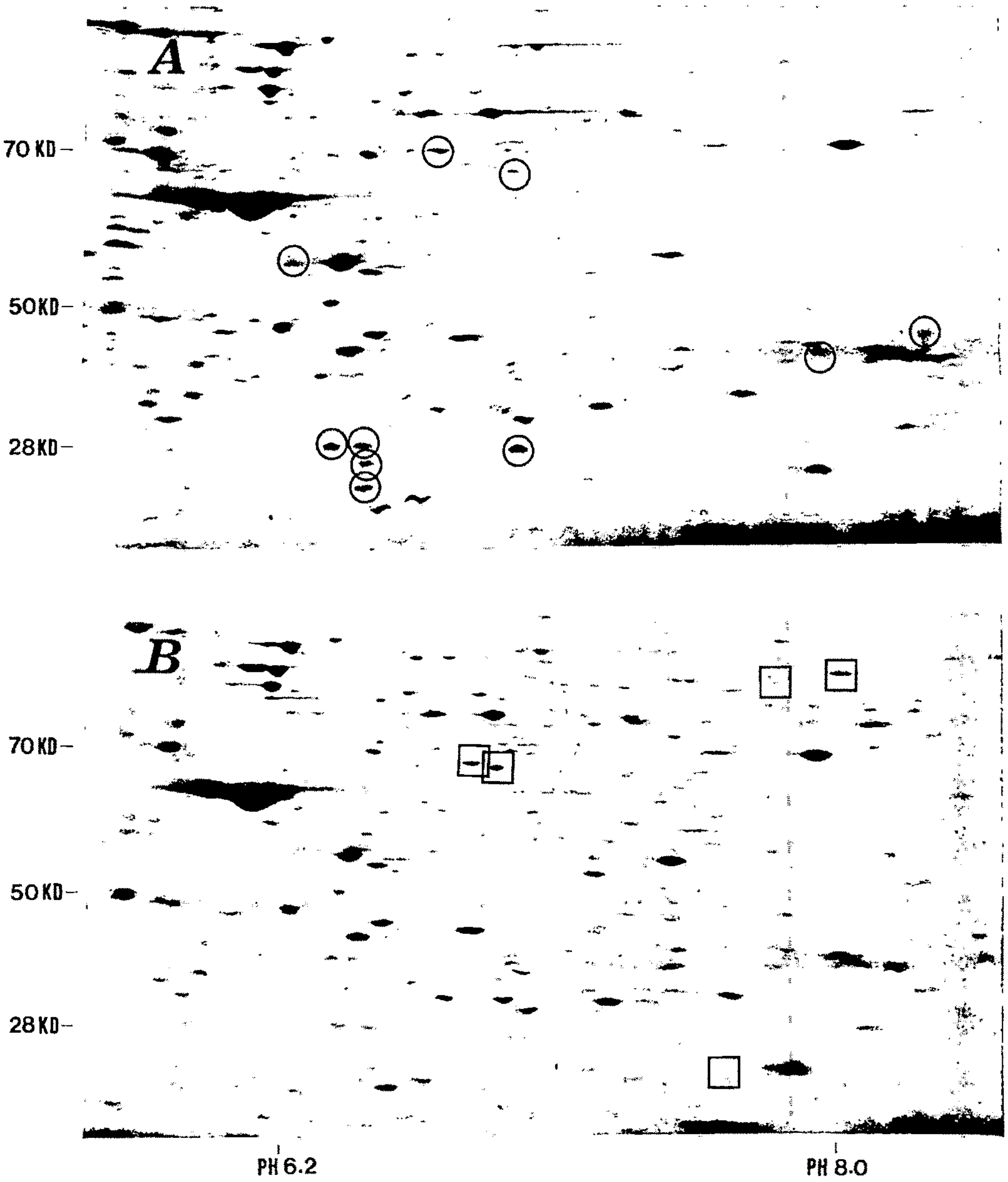
Therefore the investigation of the protein composition by electrophoretic separation methods seemed to be a proper approach to complement the results from functional assays. These techniques permit us to draw conclusions about the productive status and thus about the expression of genes in cells.

Due to the use of high resolution methods, the problem of comparing cell extracts from different noninbred animals arose. Therefore it became necessary to use homologous protein extracts to avoid differences in protein patterns caused by genetic differences.

This problem was solved by removing a part of the spleen before transplantation and preparing it for electrophoresis. This splenic extract was frozen, stored, and later used for a comparison with the extract of the homologous transplant. The differences detected between these probes now can be interpreted as specific alterations caused by the development of newly formed splenic tissue.

As a first step cell extracts from spleens and autotransplants were compared using SDS-PAGE (Fig. 1). The protein patterns of spleens and transplants were nearly identical, except in one protein (molecular weight (MW), 15 kilodalton [kd]) that was found to be produced only in spleen cells and one protein (28 kd) that was expressed in a twofold extent in the spleen. One protein (19 kd) was enriched threefold in the transplants (these quantitative estimations were done with a LKB Ultroscan gel scanner, LKB, Bromma, Sweden). After finding detectable differences with a relatively insensitive separation method such as SDS-PAGE, we performed the comparison using 2D-GE (Fig. 2).

These experiments showed that a number of proteins were produced in a much higher amount in the normal



FIGS. 2A and B. (A) Two-dimensional gelelectrophoresis (developed by silver staining) of a spleen cell extract (A) and an autotransplant extract (B). Two isoelectric points are shown in the bottom, and the molecular weight is shown on the left. Protein spots surrounded by circles are produced mainly in a high concentration in the spleen and not in the autotransplants. Spots indicated by squares are specifically enriched in autotransplants. Both gels were performed with homologous splenic and autotransplant extracts.

spleen cells than in the autotransplants, while some proteins were produced in greater amounts in the autotransplants than in the normal spleen cells.

Furthermore it could be demonstrated that the 28 kd protein class that was expressed at a higher level in the spleen consisted of three proteins with different isoelectric points.

As an additional criterion to look for alterations of proteins and/or the protein composition, the antigenic nature of proteins was used.

Polyclonal and polyspecific antisera against spleen cells and autotransplant cells enable the discrimination of the antigenicity of proteins by immunochemical assays like immunoblotting. A loss and even variations of antigenic determinants in complex mixtures are thus detectable by comparing the protein extracts with one specific antiserum.

Immunoblotting with an antiserum against nondisrupted spleen cells elicited a different immunostaining in the range of small polypeptides (molecular weight, 2 to 7 kd) in the autotransplant extract compared to normal spleens (Fig. 3). These antisera mainly contain antibodies against cell surface components. Quantification of the low molecular proteins by scanning showed that this band consisted of 24% of the total protein peaks in the autotransplants and of less than 1% in the spleens.

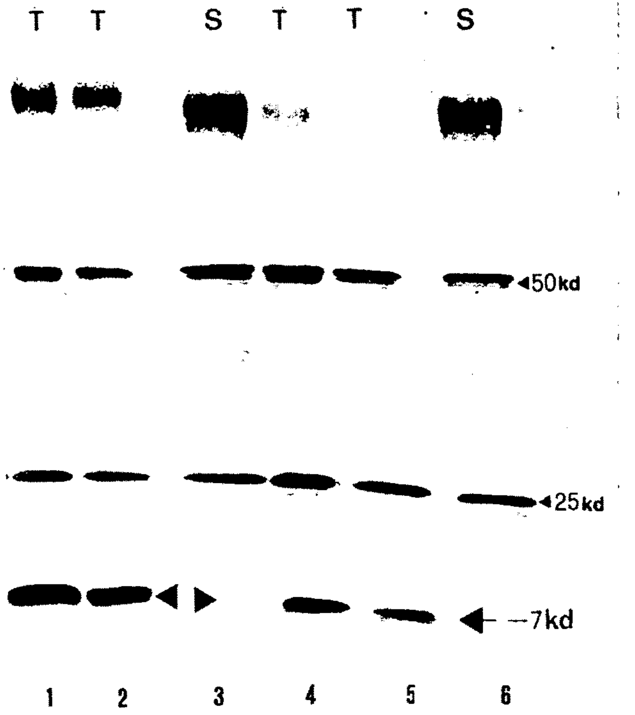
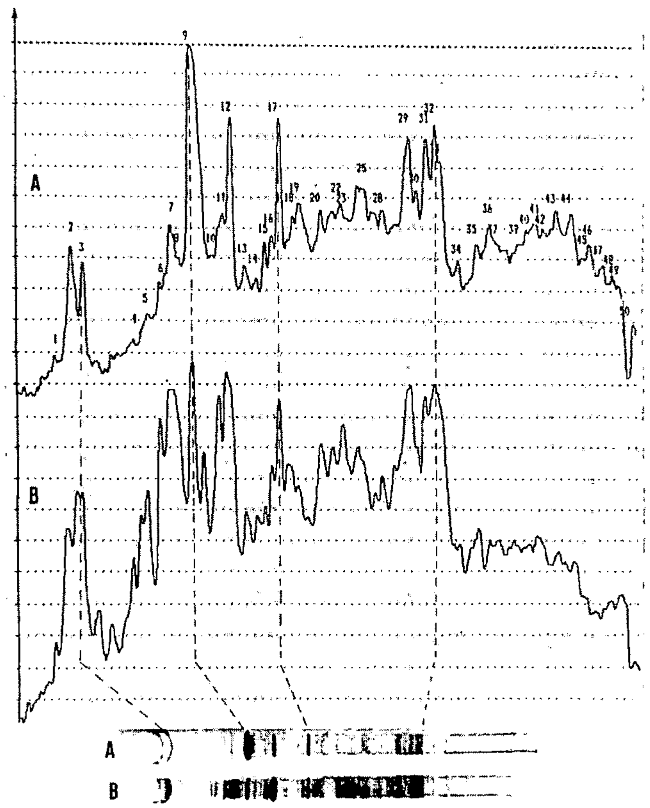


FIG. 3 Immunoblotting of spleen cell extracts (S) and autotransplants (T) with an antiserum directed against whole spleen cells. Antigenic determinants of low molecular weight (approximately 7 kd) are highly enriched in the autotransplants (indicated by arrows). The lanes 3(S) and 4(T) represent a homologous pair of extracts.



FIGS. 4A and B. Immunoblotting of spleen cell extracts (A) and autotransplants (B) with an antiserum directed against autotransplant cells. Scanning shows the different immunoreactivity of several protein bands. Peak number 9 is enriched in the spleen. Peak numbers 4 to 8, 10, 11, 12, and 18 are more concentrated in the autotransplants. Two protein bands between peak 3 and 4 are not present in the spleen extract but are in the transplants. The molecular weights of the following peaks are 3 = 5 kd, 9 = 25 kd, 17 = 31 kd, and 32 = 70 kd.

Immunization of rabbits with autotransplant cells and immunoblotting with this antiserum against both tissues also elicited differences in the concentration of the immunostaining (Fig. 4). In the 19-kd protein region the staining was increased threefold in the transplants compared to the normal spleen. This was consistent with the results from the SDS-PAGE. In contrast several bands with a molecular weight between 5 and 12 kd and two bands with 26, 28, and 33 kd showed more intensive immunostaining in the autotransplant group (demonstrated by the immunoblot scan in Figure 4) that did not correlate with the protein concentration measured by protein staining (thus indicating antigenic variations).

Discussion

Presently both the surgical procedures and the optimal site for transplantation of splenic tissue are well established. Beyond this there are many questions to be answered concerning the structure and function of the autotransplants.

Assays used for measuring splenic functions in transplants must consider quantitative and qualitative aspects. A major problem of autotransplantation of the spleen still is the low regeneration mass. Only 5% to 20% of the total original splenic mass is recovered in transplants (because it is impossible to implant the splenic tissue of the whole spleen into the greater omentum; in contrast the recovery of small amounts of implanted splenic tissue can reach 70%). Comparing the results from *in vivo* experiments such as clearing a bacteremia or measurement of the perfusion rate between spleen and autotransplants reflects these quantitative differences.

Nevertheless even small splenic transplants are able to fulfill certain functions equivalent to a normal spleen (*e.g.*, removal of Howell Jolly bodies from the blood and increase in the IgM serum level).

Therefore we decided to examine some specific immunologic functions of autotransplants such as the reaction against sheep erythrocytes and the response to mitogenic substances because these methods allow us to describe qualitative functions independent of the mass of transplants.

The B-cell response against SRBC detected by the direct hemolytic plaque assay (measurement of IgM-secreting B cells) was not reduced significantly in the autotransplant cells compared to normal spleen cells, which points to a proper environment for B-cell differentiation. In contrast the results of the mitogen stimulation demonstrated drastic differences between normal spleen cells and autotransplant cells.

For T-cell-specific mitogens such as ConA and PHA, a ten- to twentyfold increase of ^{3}H thymidine incorporation was startling. The high stimulation rate after PWM treatment (this mitogen can stimulate both cell types) may be the contribution of the mitogen- induced T cells. However the proliferation rate of B cells induced by LPS was normal. This fact also indicates a normal B-cell development in the transplants.

The abnormal T-cell proliferation can be explained by an increased number or an altered differentiation of mitogen-sensitive T-cell subclasses and/or by changes of the lymphocyte recirculation in the autotransplants.

If normal homing, recirculation, or differentiation of cells in the autotransplants is changed, it should be possible to detect these differences at the level of proteins. This was done by comparing the protein composition of both tissues. The results demonstrated that mainly two protein classes with a molecular weight of 15 kd and 28 kd, which could be separated into several proteins differing in the isoelectric point, were produced in normally detectable concentrations in the spleen cells but not in autotransplant cells. On the other hand, proteins with a molecular weight of 19 kd were overproduced in the autotransplants.

Proteins with a molecular weight within that range are β2-microglobulin, the β-chain of the class II MHC proteins, the Ia molecule, the Fc receptor, and the T3 (Leu-4) antigen. Quantitative differences in the expression of these proteins or different numbers of cells carrying these molecules can be responsible for functional alterations in autotransplant cells. Furthermore several polypeptides of autotransplant cells with different molecular weights had antigenic determinants that could be detected in a decreased concentration in the spleen cells.

This can be interpreted in two ways. Either certain classes of antigenic determinants were produced specifically in the autotransplants, or certain antigenic determinants on corresponding proteins in the spleen do not exist in a normal concentration.

The results of immunologic assays and protein separation indicate that spleen and splenic autotransplants are very similar tissues but subtle distinctions can be detected by using specific and sensitive methods.

Our data seem to be compatible with the finding that beside normal functions some alterations concerning the development of normal splenic tissue occurred in the transplants. The differences at the molecular level may be the result of general changes of the immunoarchitecture and cellular composition of the transplants. Furthermore the gels also showed slight differences concerning single protein bands between some spleens and also between transplants from different animals. These differences reflect the genetic outfit of noninbred strains. On the other hand, the alteration of the protein composition between spleens and autotransplants concerning the proteins described in this paper were consistent in all animals investigated. These results clearly indicate a general effect caused by the transplant development.

Presently we cannot decide if the differences are induced by an altered microenvironment (including soluble factors) and/or by different homing and recirculation of lymphocytes. On comparing spleen cells and autotransplant cells from other species (rabbits and rats) similar differences concerning specific immunologic functions and protein expression between both tissues could be detected (unpublished data). Therefore we conclude that the autotransplant-specific changes represent a nonspecies-specific general phenomenon.

Furthermore the autotransplantation of splenic tissue can be used as a model for studying the development and function of a complex immunologic organ. Using different tissues as transplantation sites and/or a different treatment of the transplanted cells opens many approaches to investigate the influence of the environment and other factors necessary for a normal functional development.

In conclusion we must point out that due to our results, which present a clear difference between the normal spleen and the transplants at the functional and molecular level, the general clinical application of spleen reimplantation remains questionable. Future work must be done by using inbred animals for a more detailed study of the correlation of functional assays in defined cell populations with the expression of certain proteins in both the normal spleen and autotransplants.

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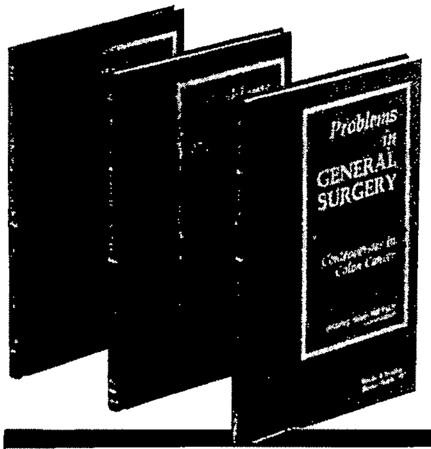

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The Preoperative and Intraoperative Hemodynamic Predictors of Postoperative Myocardial Infarction or Ischemia in Patients Undergoing Noncardiac Surgery

MARY E. CHARLSON, M.D., C. RONALD MACKENZIE, M.D., JEFFREY P. GOLD, M.D., KATHY L. ALES, M.D.,
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Among hypertensive and diabetic patients undergoing elective noncardiac surgery, preoperative status and intraoperative changes in mean arterial pressure (MAP) were evaluated as predictors of postoperative ischemic complications. Of 254 patients evaluated before operation and monitored during operation, 30 (12%) had postoperative cardiac death, ischemia, or infarction. Twenty-four per cent of patients with a previous myocardial infarction or cardiomegaly had an ischemic postoperative cardiac complication. Only 7% of those without either of these conditions sustained an ischemic complication. No other preoperative characteristics, including the presence of angina, predicted ischemic cardiac risk. Nineteen per cent of patients who had 20 mm Hg or more intraoperative decreases in MAP lasting 60 minutes or more had ischemic cardiac complications. Patients who had more than 20 mm Hg decreases in MAP lasting 5 to 59 minutes and more than 20 mm Hg increases lasting 15 minutes or more also had increased complications ($p < 0.03$). Changes in pulse were not independent predictors of complications and the use of the rate–pressure product did not improve prediction based on MAP alone. In conclusion patients with a previous infarction or radiographic cardiomegaly are at high risk for postoperative ischemic complications. Prolonged intraoperative increases or decreases of 20 mm or more in MAP also resulted in a significant increase in these potentially life-threatening surgical complications.

IN THE LAST 20 years there have been numerous studies of the risk of perioperative ischemia among patients undergoing noncardiac surgery.[1-5] Many of the studies relied on retrospective analysis of charts.[2,4,5] In a classic prospective study, Goldman developed an index to estimate cardiac risk in noncardiac surgery from preoperative characteristics after evaluating patients before operation and following patients after operation.[6,7] Several recent prospective studies evaluating risk for postoperative myocardial ischemia have used similar methods.[8-10] Some have relied on retrospective analysis of operative records[1-6] and some did not analyze intraoperative events.[8-10] Studies that recorded postoperative events in retrospect underestimated infarction rates because many postoperative infarctions are asymptomatic.[11] Patients were evaluated before operation, monitored during operation, and followed after operation with a standard protocol in two studies.[12,13] Neither of these prospective studies reported the combined impact of intraoperative hypertension and hypotension on postoperative cardiac complications.

The present study was designed to prospectively test, after taking into account prognostically important preoperative characteristics, the hypothesis that the duration of intraoperative changes in MAP of 20 mm Hg or more would predict patients who developed postoperative cardiac complications. In this study of a high-risk population of hypertensive and diabetic patients who were undergoing elective general surgery, patients were evaluated before operation, monitored by an independent observer during operation, and followed after operation for seven days with daily examinations electrocardiograms (ECG), creatine kinase (CK), and CK-isoenzymes. Postoperative ischemic events were evaluated by reviewers who were blind to the intraoperative course and preoperative patient status.

Dr. Charlson was a Henry J. Kaiser Family Foundation Faculty Scholar in General Internal Medicine. Dr. Ales is a George Morris Piersol American College of Physicians Teaching and Research Scholar.

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Methods

Assembly of Population

All patients who had essential hypertension or diabetes who were undergoing elective general surgery were eligible for enrollment. The criteria for hypertension were (1) for patients younger than 30 years, systolic pressure must be 150 mm Hg or more, or diastolic pressure must be 90 mm Hg or more; (2) for patients 30 years or older, systolic pressure must be 160 mm Hg or more, or diastolic pressure must be 95 mm Hg or more; or (3) treatment with any medication specifically employed to reduce blood pressure (*i.e.*, patients treated with diuretics for congestive heart failure alone were not considered hypertensive). Patients with secondary hypertension were excluded. The criteria for diabetes were (1) treatment with insulin or oral hypoglycemic agents, including treatment started during hospitalization; and (2) elevated fasting glucose on more than one occasion (plasma 140 mg/dL or more; whole blood 120 mg/dL or more).

Between July 1982 and September 1985, 278 patients were enrolled. To document the proportion of eligible patients who were entered into the study, the charts of all 1398 patients undergoing several types of operation (vascular surgery or cholecystectomy) during the same secular interval were reviewed; these operations accounted for 40% of the surgery performed in the prospective study. Overall of the 1398 patients who had a cholecystectomy or vascular surgery, 26% of eligible hypertensives and 34% of eligible diabetics had been entered into the prospective study (Table 1).

Preoperative Evaluation

The protocol was reviewed and approved by the Institutional Human Rights Committee. Informed consent was obtained from all patients. Before operation basic demographic and clinical data were recorded. Physical examination was performed in a standardized fashion; abnormalities in the pulmonary, cardiac, neurologic, or vascular exam were recorded. Height and weight were also recorded. The history of comorbid conditions was obtained using standardized questions and criteria. Dyspnea on exertion was quantified according to the activity that produces dyspnea (*i.e.*, walking uphill, walking one block, dressing, or talking).[14] Angina was defined as definite or probable angina according to the Rose criteria.[14] Patients with nocturnal or rest angina, or with a crescendo pattern were designated as having unstable angina. Myocardial infarction included patients who had been hospitalized for chest pain and developed either new Q waves in at least two leads that were 0.04 seconds in duration and 1 mm in depth, new ST segment depression of 1 mm or more, or new T-wave inversion that persisted for seven days, with elevation of CK or CK-MB isoenzyme. Patients who had electrocardiographic changes alone in the absence of a clinical history were not classified as having had a myocardial infarction. Congestive heart failure included patients with a definite history of pulmonary edema, paroxysmal nocturnal dyspnea, or dyspnea on exertion,[14] not in the setting of an acute myocardial infarction, arrhythmia, sepsis, and so on, who responded to treatment with digitalis, diuretics, or afterload reduction, and who required continued pharmacologic therapy. Decompensated congestive failure included those who had either an S_3 gallop on exam, evidence of congestive failure on chest x-ray, or jugular venous distention and rales on admission to the hospital. Patients with a history of intermittent claudication,[14] or a peripheral bypass procedure, and patients with an absent femoral pulse, or bilaterally absent popliteal pulses were defined as having peripheral vascular disease. Patients with documented valvular disease of any type (aortic, mitral, prosthetic valve, and so on), except mitral valve prolapse, were defined as having valvular heart disease. Patients with hemispheral symptoms, including motor deficit, sensory deficit, or homonymous hemianopsia were classified as having a cerebrovascular accident if the symptoms persisted for more than 24 hours or transient ischemic attack if the symptoms lasted 24 hours or less. Chronic pulmonary disease included patients with chronic bronchitis[14] and patients with a definite history of asthma that occurred without upper respiratory tract infections and that required pharmacologic treatment. Liver disease includes patients with a documented cirrhosis or chronic hepatitis. End organ complications of diabetes are retinopathy (aneurysms, exudates, or hemorrhages), nephropathy (biopsy or a serum creatinine of more than 2 mg/dL and a 24-hour urine protein of more than 250 mg/dL), and neuropathy (somatic: absent reflexes, sensory deficits, or amyotrophy; or visceral: nocturnal diarrhea, impotence, or orthostatic hypotension).

The patient's right and left arm sitting blood pressure and pulse, as well as the recumbent and standing pulse and blood pressure, was obtained. Blood pressure was re-

TABLE 1. *Number of Patients Who Were Eligible for the Study and the Number Who Were Entered for Two Types of Surgery Only (Cholecystectomy or Vascular Surgery)*

	Eligible	Entered	% of Eligible Who Were Entered
Hypertension			
Systolic/diastolic	59	6	10
Treatment	358	104	29
Total	417	110	26
Diabetes			
Elevated glucose	35	8	23
Treatment	73	29	40
Total	108	37	34

corded using a standard mercury manometer. Korotkoff Phase V was recorded as the diastolic pressure. The cuff was placed so that the lower margin was 2 to 3 cm above the antecubital space, with the bladder over the medial surface of the arm.[15] The adult cuff (13 × 24 cm) was employed for patients whose mid-arm circumference was less than 32 cm; the large adult for those whose circumferences was 33 cm or more but less than 42 cm. Blood pressures were obtained every 4 hours before surgery by the nursing staff. These systolic and diastolic blood pressures were recorded to delineate the patient's usual preoperative MAP, the standard deviation of the MAP, and the minimum and maximum MAP.

Basic preoperative laboratory values were recorded, including hemoglobin, electrolytes, urinanalysis, creatinine, CK, ECG, and chest x-ray.

Intraoperative Monitoring

On the day of surgery, a research assistant, blinded to the hypotheses of the study, accompanied the patient to the operating room and recorded pulse and blood pressure during induction and intubation and every five minutes thereafter, using either an intra-arterial catheter (at the discretion of the anesthesiologist), a mercury manometer, or an indirect automatic device. In 52 patients intra-arterial measurements were made using a 20-gauge teflon catheter in the radial artery that was connected to a Marquette 7000 dual-pressure monitor calibrated before each use (accuracy of ± 1 mm Hg). In 76 patients the Omega 1000, an indirect oscillometric blood pressure recorder, was used (accuracy of ± 2 mm Hg); the large adult cuff (15 × 33 cm) was used if the arm circumference was 30 cm or more. The oscillometric device has been shown to produce reproducible and valid measurements of blood pressure while used in the operating room.[16] In 150 patients the anesthesiologist decided to use standard mercury manometer instead of the Omega 1000. In these cases the research assistant obtained and recorded the blood pressures according to the procedures described previously. To standardize the definition of the MAP with the different techniques, MAPs were calculated as the diastolic pressure + 1/3 (systolic–diastolic.)

The primary analysis of intraoperative blood pressures was based on the differences between the intraoperative MAPs and the preoperative MAPs, after adjusting for differences between arms. Hypotension was defined as an intraoperative MAP that was 20 mm Hg or more below the patient's preoperative MAP. Similarly hypertension was defined as an intraoperative pressure that was 20 mm Hg or more above the patient's preoperative baseline.

The research assistant recorded all pharmacologic agents used during each five-minute interval of the operation. The use of anesthetic agents and adjuvants such as thiopental, nitrous oxide, fentanyl, droperidol, d-tubocurarine, pancuronium, succinylcholine, and atracurium were recorded. The use of pressors (*e.g.*, phenylephrine, dopamine, ephedrine, norepinephrine, and so on), antihypertensive agents (*e.g.*, hydralazine, nitroprusside, beta blockers, nitropaste) and other agents such as mannitol, lasix, or lidocaine were also noted. Major intraoperative events, such as skin incision, reversal of anesthesia, aortic cross-clamping, drainage of ascites, and changes in position were also recorded. All input and output was recorded at 60-minute intervals; net intake was calculated on an hourly basis. The specific fluids used and the total output during the operation (*e.g.*, suction, sponges, nasogastric drainage, urine output, or placement of a foley catheter) were also recorded. Ringers lactate, 0.9% saline, D_5 Ringers lactate, and Normosol (Abbott Laboratories, North Chicago, IL) were considered isotonic saline; D_5W, D_5 ¼ normal saline and D_5 ½ normal saline were not. Hourly rates of infusion were calculated on the amount of time required for surgery.

Postoperative Follow-up

All patients were followed daily for seven days after operation or until death, discharge, or reoperation with clinical examinations, serum creatinines, ECGs, CK, and CK isoenzymes. Patients who underwent reoperation were considered censored in terms of follow-up at the time of reoperation.

The CKs were immediately frozen and assayed in batch using a technique based on the methods of Rosalki[17] when 100 samples were available. Isoenzymes were measured if the CK was more than 100 U/L. The initial 20% of the specimens were assayed using anion exchange beads.[18] The laboratory then switched to agarose electrophoresis.[19] The two techniques appeared reasonably comparable within the cut-offs used for the 76 samples used to compare the methods (kappa = 0.51).

All postoperative ECGs were read by two reviewers who were blinded to all aspects of the preoperative status of the patient except for their preoperative ECG; they were also blinded to the intraoperative course and all aspects of the postoperative course except for the ECGs. Disagreements were resolved by a third blinded reviewer. All postoperative ECGs were read in relation to the preoperative baseline ECG. Changes in the ST segment or T waves must all have occurred in at least two leads in the absence of new electrolyte abnormalities or the new use of digitalis. Details of the ECG classification have been published;[7] in brief patients were classified as having (1) new Q waves that were 0.03 seconds or longer in duration and more than 1 mm in depth in two leads; (2) unequivocal ST elevation 2 mm or more in comparison to the baseline ECG; (3) new ST depression of 2 mm or more. If there was pre-existing ST depression, the new depression must have added an additional 2 mm with or without T-wave inversion; and (4) new inversions of previously upright T waves.

The postoperative course of any patient who developed any of the above changes in their ECG or new bundle branch block or arrhythmia was reviewed by two physicians who were blind to the patient's preoperative status and intraoperative course. Patients who had any episode of chest pain, tightness, or discomfort lasting 30 minutes or more, palpitations, or syncope, or whose surgeon suspected that the patient had a myocardial infarction failure also were evaluated by the reviewers. These physician reviewers determined whether the patients who were suspected of having postoperative myocardial ischemia or infarction met the diagnostic criteria.

Definition of Postoperative Infarction and Ischemia

The criteria for myocardial infarction and ischemia[20] were provided to our blinded reviewers and they made the final designation. For example there were six patients who either had new q waves or major consistent ECG change persisting for more than 48 hours associated with 5% or more MB. The one patient with new q waves and one patient with ST-T changes lasting 48 hours or more, with 5% or more MB were designated as having a definite myocardial infarction. None of the four patients with T-wave inversions lasting ≥48 hours or more with 5% or more MB were rated by the reviewers as having a definite myocardial infarction. One patient with ST-T changes that lasted less than 48 hours with 5% or more MB was designated as having a definite infarction. For the sake of clarity, the patients who were finally designated as having definite, probable, or possible myocardial infarction or definite ischemia will be described. The reviewers also classified deaths and arrests as cardiac or noncardiac. A cardiac death was a death in the setting of myocardial ischemia, infarction, ventricular tachycardia, cardiogenic shock, with the clinical events leading to death compatible with a primary cardiac etiology.

Cardiac deaths. There were four cardiac deaths, one of which occurred after intraoperative ventricular tachycardia, one following anginal episode, one after refractory arrhythmias and cardiogenic shock, and one after developing a new Q wave, followed by an arrest.

Cardiac arrest. Two arrests that did not lead to cardiac death occurred in the setting of pulmonary edema and symptomatic myocardial ischemia. Two arrests occurred in the setting of a definite or possible myocardial infarction: one with ST-T depression 48 hours or more with 12% MB (definite), and the other with ST elevation less than 48 hours with 6% MB (possible).

Definite or probable myocardial infarction. There was one definite myocardial infarction without an arrest or death: a patient with ST-T depression less than 48 hours with 5% MB. There were two patients with probable myocardial infarction: one patient had new T inversion more than 48 hours with 25% MB and another had new T inversion more than 48 hours with 8% MB.

Possible infarction and definite ischemia. There were three patients with possible myocardial infarctions, 1 with ST-T depression more than 48 hours with 4% MB, 1 with ST normalization more than 48 hours with 5% MB, and 1 with T inversion more than 48 hours with 5% MB.

There were 18 patients designated as having definite ischemia with ECG changes: 1 patient with T inversion more than 48 hours and 5% MB and 1 with 3% to 4% MB; 1 patient with ST elevation more than 48 hours and 3% to 4% MB and 1 patient with ST elevation less than 48 hours and more than 5% MB; 1 patient with ST normalization more than 48 hours and 3% to 4% MB; 4 patients with ST depression and T wave inversion more than 48 hours with 0% to 2% MB; and 5 patients with T depression more than 48 hours with 0% to 2% MB. One patient had unstable angina without ECG changes, and three patients had definite angina by the Rose criteria.

Listing events hierarchically, among the 278 patients there were 4 cardiac deaths, 4 cardiac arrests, 3 definite or probable myocardial infarctions, 3 possible infarctions, 14 definite ischemias, and 4 anginas.

In 24 (8.6%) of the patients, the research assistant was not present in the operating room to record events and blood pressures. Among those patients, 1 (4%) suffered cardiac death, 1 had a possible infarction, 1 had definite ischemia, and 1 had definite angina. Because the purpose of this analysis is to assess the intraoperative blood pressures and events in relation to cardiac complications, we have omitted these 24 patients and these four cardiac events from this analysis because the intraoperative data was not recorded by an independent observer. The remainder of the paper will concentrate on the 254 patients, for whom intraoperative data was recorded by an independent observer. However, when the 24 patients were included in the analysis, the results did not differ.

Analysis

The preoperative pressures were all obtained by mercury manometer and the intraoperative pressures were obtained either by mercury manometer (n = 121), intra-arterial catheter (n = 51), or indirect oscillometric device (n = 71). Because there are some systematic differences in the systolic, diastolic, and mean pressures obtained using the different techniques,[16] the analysis was performed in several ways. First the differences in MAPs were evaluated without any adjustment. Second the MAPs were evaluated after adjustment for the systematic differences between methods of measurement. For example the mean intra-arterial pressure was 3.4 mm Hg lower than simultaneous assessments with a mercury manometer; thus for the adjustment 3.4 was added to all intraoperative pressures obtained by arterial catheter. Similarly the Omega mean pressure was 0.4 mm Hg lower than the mercury manometer pressure, so 0.4 was added to all pressures obtained using the Omega device. Second the intraoperative MAPs were also adjusted using the regression equations developed in a study comparing the devices;[16] however for the added complexity, there was no particular advantage of using regression instead of the simpler method of adjustment. Therefore the results are presented with the first method of additive adjustment. The rate–pressure product was calculated as the pulse multiplied by the MAP.

Logistic regression was performed using PROC LOGIST, available in the Statistical Analysis System.[21] For logistic regression at least five to ten outcome events must be available for each variable examined.[22,23] Therefore only four or five covariates could be evaluated. The approach developed by Harrell for creating clusters of related phenomena before evaluation using logistic regression was used to reduce the number of separate variables examined.[22]

Results

Four per cent (10 of 254) of the patients had a perioperative cardiac death, cardiac arrest, or a definite or probable myocardial infarction. Eight per cent (20 of 254) had a possible myocardial infarction or definite myocardial ischemia. Thus 12% of patients had a perioperative ischemic cardiac event. Most of these events occurred within the first three days after surgery, with the risk declining sharply after the second postoperative day.[24]

Table 2 shows the ischemic complications according to the duration of increases and decreases of 20 mm Hg or more in intraoperative MAP. At the beginning of the study, the hypothesis was that this magnitude of change in MAP would be associated with increased cardiac complications. Sixty per cent of patients had intraoperative increases (154 of 254) and 62% (159 of 254) had decreases of this magnitude. However ischemic complications were increased in only two groups of patients: 19% among the 43 patients who had decreases in MAP lasting 60 minutes or more (p = 0.03); and 20% among the 41 patients with decreases in MAP lasting 5 to 59 minutes who also had increases in MAP for 15 minutes or more (p = 0.02).

The complication rates were also evaluated with definitions of changes in MAP used in other studies.[7,12,13] An intraoperative fall in blood pressure of 50% or more occurred in 15 patients; 15% of these patients had ischemic complications. A fall of 33% for ten minutes or more occurred in 36 patients; 19% had complications. Similarly 14% of 56 patients who had intraoperative diastolic pressures rise over 110 and 17% of 41 patients whose systolic pressures rose over 200 had ischemic complications.

Table 3 shows the total rates of perioperative cardiac death, arrest, myocardial infarctions or ischemia according to the preoperative characteristics of the patients. The third column shows that total ischemic cardiac complication rates were increased among patients with severe hypertension (23%), those with previous myocardial infarction (27% and 22%), those in Canadian cardiovascular classes III-IV (22%), those with chronic renal disease (27%), with left ventricular hypertrophy on ECG (23%), or cardiomegaly on chest x-ray (24%). As might be anticipated, there was considerable correlation between these findings. For example when the complication rates for patients with left ventricular hypertrophy on ECG or cardiomegaly on chest x-ray were analyzed jointly, cardiomegaly on chest x-ray had the predominant impact: patients with left ventricular hypertrophy by ECG without cardiomegaly on chest x-ray did not have higher complication rates. Among patients with cardiomegaly the higher rates were not attributable to congestive heart failure; the rates were essentially identical among the 36 patients with cardiomegaly without congestive failure (25%) and the 14 patients with congestive failure (21%).

Patients with preoperative angina did not have a higher rate of ischemic cardiac complications. The slightly higher

TABLE 2. *Rates of Postoperative Myocardial Infarction, Ischemia, Cardiac Arrest or Death According to the Duration and Magnitude of Intraoperative Changes in Mean Arterial Pressure in Relation to Preoperative Baseline*

Intraoperative MAP Rises ≥ 20 mm Hg Above Baseline	Intraoperative MAP Falls ≥ 20 mm Hg Below Baseline				
	None	5–14 Minutes	15–59 Minutes	≥60 Minutes	Total
None	12% (33)	12% (8)	6% (32)	15% (27)	11% (100)
5–14 minutes	7% (28)	18% (11)	4% (24)	30% (13)	12% (76)
≥15 minutes*	6% (34)	26% (19)	14% (22)	0% (3)	13% (78)
Total	9% (95)	18% (38)	7% (78)	19% (43)	11% (254)

* There were 7 patients with increases lasting >60 minutes.

TABLE 3. *Perioperative Cardiac Death, Arrest, Myocardial Infarction, and Ischemia According to Preoperative Characteristics of Patients*

Preoperative Characteristics	Cardiac Death Arrest or Definite MI (%)	Probable MI or Definite Ischemia (%)	Total (%)	Number of Patients
Age				
<70	2	9	11	(162)
≥70	7	6	13	(92)
Sex				
Male	6	9	15	(97)
Female	3	7	10	(157)
Hypertension				
Not severe	3	8	11	(152)
Severe*	8	15	23	(39)
Diabetes				
No end organ damage	7	5	12	(73)
End organ damage	4	11	15	(27)
Dyspnea				
Walk without stopping for breath	3	7	11	(179)
Stop while walking	2	9	11	(56)
Short of breath dressing	16	11	27	(18)
12-minute walking distance				
≥640 meters	5	6	11	(17)
400–640 meters	2	7	9	(55)
<400	9	13	22	(45)
Not done	3	6	9	(137)
Cardiac comorbidity				
Angina	6	8	14	(48)
Myocardial infarction				
<6 months	9	18	27	(11)
≥6 months	18	4	22	(22)
Congestive heart failure				
Compensated	5	11	16	(18)
Decompensated	0	0	0	(14)
Valvular heart disease	7	4	11	(27)
Goldman's cardiac risk class				
Class I	3	8	11	(146)
Class II	4	8	12	(76)
Class III/IV†	6	10	16	(32)
Canadian cardiovascular classification				
I	3	8	11	(217)
II	6	7	13	(15)
III–IV	11	11	22	(22)
Other comorbidity				
Peripheral vascular disease	4	5	9	(92)
Cerebrovascular accident	6	7	13	(31)
Chronic bronchitis	3	7	10	(63)
Chronic renal disease	9	18	27	(22)
Comorbidity index				
0–2	5	5	11	(163)
3–4	5	5	10	(73)
>5	11	11	22	(18)
Electrocardiogram				
Q waves on EKG	5	3	8	(38)
Infarct on EKG	10	6	16	(64)
Any abnormality	10	8	18	(84)
Left ventricular hypertrophy‡	11	12	23	(26)
APC's or VPC's on EKG	0	8	8	(12)
Chest X-ray				
Cardiomegaly‡	6	18	24	(50)

* History of diastolic blood pressures > 120 mm Hg or hospitalization for hypertension.

† Only two patients were in class IV.

‡ Definite and probable.

rates among patients with ECG evidence of infarction were attributable to patients who also had a clinical history of an infarction; among patients whose ECG provided the only evidence of a previous infarction, the complication rate was only 9%. Similarly once the history of a previous infarction was taken into account, patients with an abnormal ECG did not have increased complication rates. The higher rate of complications in cardiac risk class III-IV was similarly attributable to patients with a previous infarction; 22% (n = 23) of those with a previous MI in class I-II, and 30% (n = 10) in class III had ischemic complications. The higher rates in Canadian cardiovascular class III-IV were also attributable to patients with a previous infarction.

Once the presence of cardiomegaly was taken into account, severe hypertension was not an independent predictor of ischemic complications. Cardiomegaly was found in 36% of patients with severe hypertension, but in only 19% of patients without severe hypertension. Among the 39 severe hypertensives, 38% of the eight patients with a previous myocardial infarction and 20% of the ten patients with cardiomegaly but without infarction had ischemic complications. Among 21 severe hypertensives without cardiomegaly or infarction, the complication rate was only 14%. Logistic regression confirmed that among the preoperative characteristics of patients, only previous myocardial infarction ($p = 0.055$) and cardiomegaly ($p < 0.01$) were independent predictors of ischemic complications.

Table 4 shows the patients stratified hierarchically according to whether they had a previous infarction or cardiomegaly and according to intraoperative changes in MAP. Overall 7% of patients without cardiomegaly or previous myocardial infarction, but 25% of those with one of those conditions had cardiac complications. The ten patients who had both cardiomegaly and previous myocardial infarction who had a 20% postoperative ischemic complication rate were grouped together with the 23 patients who had a previous myocardial infarction but

TABLE 4. *Ischemic Cardiac Complications According to Preoperative Characteristics and Intraoperative Changes in MAP*

A. Patients Without Previous Myocardial Infarction or Cardiomegaly

Intraoperative MAP Rises ≥20 mm Hg Above Baseline	Intraoperative MAP Falls ≥20 mm Hg Below Baseline			
	None	5–59 Minutes	≥60 Minutes	Total
0–14 minutes	3% (40)	6% (52)	11% (26)	6% (118)
≥15 minutes	0% (27)	16% (32)	0% (4)	8% (63)
Total	1% (67)	10% (84)	10% (30)	7% (181)

B. Patients with Cardiomegaly Without Infarction

Intraoperative MAP Rises ≥20 mm Hg Above Baseline	Intraoperative MAP Falls ≥20 mm Hg Below Baseline			
	None	5–59 Minutes	≥60 Minutes	Total
0–14 minutes	18% (11)	8% (13)	44% (9)	21% (33)
≥15 minutes	25% (4)	67% (3)		43% (7)
Total	20% (15)	19% (16)	44% (9)	25% (40)

C. Patients with Previous Myocardial Infarction*

Intraoperative MAP Rises ≥20 mm Hg Above Baseline	Intraoperative MAP Falls ≥20 mm Hg Below Baseline			
	None	5–59 Minutes	≥60 Minutes	Total
0–14 minutes	33% (9)	10% (10)	40% (5)	25% (24)
≥15 minutes	33% (3)	16% (6)		22% (9)
Total	33% (12)	13% (16)	40% (5)	24% (33)

* Includes 23 patients with previous myocardial infarction alone and 10 patients with both previous MI and cardiomegaly.

Model $X^2 = 19.01$; $p < 0.001$; $R = 0.244$

	Beta	p
Myocardial infarction	0.95 ± 0.49	p = 0.055
Cardiomegaly	1.14 ± 0.44	p = 0.01

	Beta	p
≥20 mm Hg decreases in MAP ≥60 min.	1.09 ± 0.49	p = 0.03
≥20 mm Hg decreases in MAP <60 min. *and* ≥20 mm Hg increases in MAP >15 min.	1.19 ± 0.51	p = 0.02

who did not have cardiomegaly. Twenty-six per cent of these latter patients had a postoperative ischemic event. When these preoperative characteristics are taken into account, the same pattern emerged, as was apparent in Table 1. Patients with 5 to 59 minutes of decreases in MAP (p = 0.03) and those with less than 60 minutes of decreases who also had 15 minutes or more of increases in MAP (p = 0.02) had higher complication rates. Patients with either cardiomegaly or previous infarction who had more than 60 minutes of low MAPs had particularly high complication rates—40% to 44%. There were no important differences in the percentage of patients with cardiomegaly or previous infarction who had 60 minutes or more of decreased MAPs in relation to those without either condition, but these patients did not tolerate such changes.

Table 5 shows the ischemic complications in relation to the type of operation and anesthesia, the length of surgery, intraoperative events, medications, fluid management, and intraoperative changes in pulse. The ischemic complication rates were slightly but not significantly higher among patients who underwent general anesthesia because of a higher proportion of patients with previous myocardial infarction or cardiomegaly in this group. The patients who had narcotic agents (*e.g.*, fentanyl with nitrous oxide) used as the primary anesthetic were included in this group; however there were too few patients to evaluate its impact on postoperative ischemic complications. The complication rates were higher among patients who underwent abdominal, peripheral vascular, or aortic aneurysm surgery. Not surprisingly, among patients who had aortic aneurysm repair, 40% (10 of 25) had cardiomegaly or a previous infarction. However aneurysm patients did not experience complications unless they had important changes in intraoperative MAP: of 11 patients who had prolonged (60 minutes or more) decreases in MAP, 36% had complications; and of the eight patients who had increases and decreases in MAP, 38% had complications. Only six patients undergoing aneurysm repair did not have either of these hemodynamic patterns.

Among patients who did not have major intra-abdominal or vascular surgery, complications occurred only among patients who had either cardiomegaly (22%; n = 9) or previous myocardial infarction (33%; n = 9). Once intraoperative hemodynamic patterns were taken into account, patients with longer operations did not have higher complication rates—although obviously patients with longer operations had a greater opportunity for prolonged changes in MAP. Although patients who received vasoactive agents or fluid challenges appear to have higher complication rates, when the preoperative characteristics and intraoperative hemodynamic patterns were taken into account, those receiving any of these interventions had complication rates similar to those of other patients in the same group. Although the numbers involved were small, the impact of such interventions appeared to depended on the hemodynamic result (*i.e.*, whether prolonged hypotension or hypertension was avoided). Ischemic complication rates did not vary significantly according to net fluid intake or net hourly blood loss; patients with larger hourly urine output did have a higher rate of ischemic complications, although this did not reach significance.

Table 6 shows the cardiac complication rates in relation to the preoperative characteristics, changes in intraoperative MAP, and to intraoperative changes in pulse of more than 20 beats per minute. In this table the intraoperative changes in blood pressure were reduced to the three important groups: prolonged decreases (≥60 minutes), increases of 15 minutes or more and decreases of 5 to 59 minutes, and patients with neither of those patterns. There were only eight patients who had both intraoperative increases and decreases of 20 or more beats per minute in pulse; they have been included with the patients whose pulse decreased. Pulse increases or decreases did not carry increased risk of developing cardiac complications when other variables were taken into account, except among patients with a previous myocardial infarction. Among patients with a previous infarction, only 6% of 16 patients without pulse changes had a postoperative ischemic complication, while 41% of the 17 patients who had either an increase or decrease in pulse of 20 or more beats per minute had complications. The changes in pulse and MAP that were examined in this table were not simultaneous; that is the changes in MAP occurred in different time intervals than the changes in pulse.

To evaluate the impact of simultaneous changes in intraoperative pulse and MAP, the changes in the intraoperative rate–pressure product (MAP × pulse) were also examined. Table 7 shows ischemic complications according to whether patients had 20% or more increases or decreases in the rate–pressure product. The major finding was that patients who had a decrease of 20% or more in the rate–pressure product for more than 30 minutes had greater complication rates. Table 8 shows ischemic complications according to whether patients had 20% or more increases or decreases in intraoperative rate–pressure product that lasted for 30 minutes or more according to the preoperative characteristics. The predominant finding was that patients with cardiomegaly or previous infarction had increased complications when they had intraoperative decreases in rate–pressure product that lasted for more than 30 minutes.

Discussion

The preoperative characteristics of patients likely to experience postoperative ischemia after noncardiac surgery have been studied by a number of investigators. Previous

TABLE 5. *Perioperative Cardiac Death, Arrest, Myocardial Infarction, and Ischemia According to Type and Duration of Operation, Anesthesia, and Intraoperative Events*

	Cardiac Death Arrest or Definite MI (%)	Probable MI or Definite Ischemia (%)	Total (%)	Number of Patients
Type of operation				
Peripheral vascular	5	5	11	55
Aortic aneurysm	8	20	28	25
Abdominal	2	10	12	96
Other operations	4	2	6	78
Length of operation				
<2 hours	3	3	6	79
≥2 < 4 hours	4	9	13	110
≥4 hours	6	11	17	65
Type of anesthesia				
Local or regional	4	0	4	27
Spinal or epidural	5	5	10	20
General	4	9	13	207
Intraoperative events				
Aortic cross clamping	8	14	22	27
Cardiac arrest	100	0	100	2
Intraoperative medications				
Any hypotensive agent*	7	14	21	28
Any pressor†	4	11	15	26
Pressors & hypotensive agents	29	0	29	7
Fluid challenge‡				
No	3	7	9	216
Yes	8	16	24	38
Hourly blood loss				
0–49 cc/hour	3	7	10	119
50–99 cc/hour	6	8	14	35
100–249 cc/hour	4	8	12	59
≥250 cc/hour	4	10	14	41
Hourly urine output				
0–49 cc/hour	3	4	7	136
50–99 cc/hour	2	10	12	41
>100 cc/hour	8	14	22	49
No Foley	4	14	18	28
Net intraoperative fluid infusions§				
<300 cc/hour	2	9	11	45
300–499 cc/hour	7	10	17	42
500–749 cc/hour	7	3	10	41
750–999 cc/hour	4	10	14	46
≥1000 cc/hour	3	7	10	60
Intraoperative pulse change of ≥20 beats				
Decrease in pulse‖	7	8	15	69
Increase in pulse				
5–14 minutes	5	2	7	44
≥15 minutes	0	14	14	55

* Hydralazine, nitroprusside, beta-blocker, nitropaste.

† Neosynephrine, ephedrine, dopamine, norepinephrine.

‡ >500 cc in 15 minutes or 1000 cc in 30 minutes.

§ Isotonic saline, Ringer's lactate, D_5 Ringer's lactate, Normosol.

‖ No decrease in pulse of >20 beats lasted longer than ten minutes.

studies have agreed that patients with a previous myocardial infarction, particularly those who had an infarction within 6 months of surgery, are at increased risk for postoperative infarction,[4-7,12,13,25] while those with angina alone were not.[6,7,12] Several studies have found that the risk of ischemic events was higher among patients with greater functional impairment.[7,8,26] Age over 70 years, shortness of breath, mitral regurgitation, more than 5 PVCs per minute, and a tortuous or calcified aorta were identified by Goldman[7] as risk factors for postoperative myocardial infarction. Most patients who had either a cardiac death or postoperative infarction had either pre-

TABLE 6. *Ischemic Complications According to History of Previous Infarction and Cardiomegaly, Intraoperative Changes in MAP, and Intraoperative Changes in Pulse*

	Intraoperative Changes in Pulse			
Intraoperative Changes in MAP ≥20 mm Hg	None	Any Increase ≥20 Beats	Any Decrease ≥20 Beats	Total
	A. Patients Without Cardiomegaly or Previous Infarction			
Neither	4% (49)	5% (40)	0% (30)	3% (119)
Increase ≥15 minutes and decrease ≥5 minutes	11% (9)	12% (16)	29% (7)	16% (32)
Decrease ≥60 minutes	0% (11)	22% (9)	10% (10)	10% (30)
Total	4% (69)	9% (65)	6% (47)	7% (181)
	B. Patients with Cardiomegaly Without Infarction			
Neither	23% (13)	13% (8)	0% (7)	14% (28)
Increase ≥15 minutes and decrease ≥5 minutes		100% (1)		100% (1)
Decrease ≥60 minutes	50% (6)	0% (1)	50% (4)	36% (11)
Total	31% (19)	20% (10)	18% (11)	24% (40)
	C. Patients with Previous Infarction			
Neither	9% (13)	40% (5)	50% (4)	23% (22)
Increase ≥15 minutes and decrease ≥5 minutes	0% (2)	0% (2)	50% (2)	16% (6)
Decrease ≥60 minutes	0% (1)	100% (1)	33% (3)	40% (5)
Total	6% (16)	38% (8)	44% (9)	24% (33)

operative congestive heart failure or ischemic heart disease.[7] Congestive heart failure was identified as a risk factor in another study.[13] In this study, which consisted mainly of hypertensive and diabetic patients, those with a previous myocardial infarction and those with greater functional impairment had increased ischemic complications, but age and congestive heart failure were not significant risk factors. The number of patients with PVCs on preoperative ECG or mitral regurgitation was too small to draw any conclusions. Because the majority of our patients had hypertension, a substantial proportion of patients had cardiomegaly on chest x-ray or left ventricular hypertrophy on ECG. Goldman found that 8% of patients with cardiomegaly had postoperative infarction or cardiac death, in contrast to 2% of patients without cardiomegaly; however this difference did not retain significance in a multivariate analysis.[7] In this study cardiomegaly was a significant predictor of ischemic complications.

The type and duration of operation have also been evaluated as predictors of ischemic complications. Patients undergoing upper abdominal or intrathoracic surgery were found to be at higher risk for cardiac death or infarction in several retrospective[4,5] and one prospective study;[13] but this was not confirmed in two other prospective studies.[7,12] In the earliest studies[1,2] the duration of surgery was related to ischemic complications, but later studies[7,12,13] have not confirmed this. In this study the type and duration of surgery did not predict ischemic complications once hemodynamic events during surgery were taken into account.

In most studies of noncardiac surgery, patients who had intraoperative hypotension, defined as a 30% decrease

TABLE 7. *Perioperative Cardiac Death, Cardiac Arrest, Myocardial Infarction, or Ischemia According to Intraoperative Changes in the Rate-Pressure Product*

	≥20% Decrease in the Rate-Pressure Product				
≥20 Increase in the Rate-Pressure Product	<5 Minutes	5–29 Minutes	30–59 Minutes	≥60 Minutes	Total
<5 minutes	0% (11)	7% (14)	0% (6)	20% (40)	13% (71)
5–29 minutes	9% (23)	4% (28)	18% (23)	12% (33)	10% (107)
30–59 minutes	7% (15)	10% (10)	20% (5)	20% (5)	11% (35)
≥60 minutes	18% (22)	7% (15)	—	50% (4)	15% (41)
Total	10% (71)	6% (67)	15% (34)	18% (82)	11% (254)

TABLE 8. *Perioperative Ischemic Complications According to History of Previous Infarction and Cardiomegaly and Intraoperative Changes in Rate-Pressure Product*

≥20% Increase in the Rate-Pressure Product	≥20% Decrease in the Rate-Pressure Product		
	<30 Minutes	≥30 Minutes	Total
A. Patients Without Cardiomegaly or Previous Infarction			
<30 minutes	4% (55)	9% (69)	8% (124)
≥30 minutes	8% (48)	0% (9)	7% (57)
Total	6% (103)	8% (78)	7% (181)
B. Patients with Cardiomegaly Without Infarction			
<30 minutes	9% (11)	32% (19)	23% (30)
≥30 minutes	25% (8)	50% (2)	30% (10)
Total	16% (19)	33% (21)	25% (40)
C. Patients with Previous Infarction			
<30 minutes	10% (10)	29% (14)	21% (24)
≥30 minutes	16% (6)	67% (3)	33% (9)
Total	13% (16)	35% (17)	24% (33)

in the systolic pressure, have had higher postoperative ischemic complications,[1-4,12] particularly if the hypotension was prolonged.[3] One study found that such changes predicted cardiac death, but not infarction.[7] Only two studies of noncardiac surgery specifically evaluated the impact of intraoperative hypertension, and neither found increased complications with hypertension.[7,13] Goldman did examine patients who had both intraoperative hypertension (systolic pressure of 200 mm Hg or more, or more than 40 mm higher than preoperative systolic pressure) and hypotension (33% fall in intraoperative systolic pressure) and found that such patients did not have an increased risk of complications. In this study both intraoperative hypotension and hypertension were defined in terms of the MAP. Patients with 60 minutes or more of 20 mm Hg or more decrease in MAP were at increased risk. Patients with 15 or more minutes of 20 mm Hg or more increases in MAP and 20 mm Hg or more decreases in MAP lasting less than 60 minutes were at increased risk for ischemic complications. Intraoperative changes in pulse were less helpful in identifying patients at risk, with the important exception of patients with a previous infarction. The rate–pressure product was also evaluated, although the rate–pressure product has been criticized as a potentially misleading method of assessing intraoperative myocardial oxygen consumption because of the differential impact of changes in pressure and pulse in the anesthetized patient.[27-29]

Intraoperative decreases in pressure occur almost universally during inhalation anesthesia because halothane, isoflurane, and enflurane all produce a dose-related depression of myocardial contractility.[30-33] With inhalation anesthesia hypertensives, especially those with left ventricular hypertrophy, are prone to the development of intraoperative hypotension, which occurs as a result of decreased systemic vascular resistance and vasodilation of capacitance vessels.[34] This is a potential explanation for the greater risk of ischemic complications among patients with cardiomegaly. Intraoperative hypotension is known to occur as a result of surgical stimulation (*e.g.*, skin incision)[35,36] and unclamping of the aorta.[37] Apart from surgical events, Prys-Roberts et al.[38] have also show that intraoperative hypocapnia may produce an increase in systemic vascular resistance, a fall in cardiac output, and resultant hypotension. This effect is more pronounced in the hypertensive than in the normotensive patient because of the greater reactivity of smooth muscle in the hypertensive patient.[38] Intraoperative hypertension was relatively common in this study because of the substantial proportion of hypertensive patients. Hypertensives have an exaggerated increase in pressure during anesthesia to noxious stimuli.[32-34] Thus the large proportion of hypertensives in the study probably increased the rate at which intraoperative hypotension and hypertension occurred.

Evidence has emerged from studies of patients undergoing noncardiac surgery that used continuous monitoring devices to record intraoperative ECGs linking intraoperative hypertension[39-41] and tachycardia[40,41] with ST-T segment changes. In these studies no reference was made to relationships between ST-T depression and hypotension. However the data supports other studies in hypertensives that such hemodynamic changes may precipitate myocardial ischemia.[32,33,38]

Efforts to prevent perioperative ischemic complications among hypertensives and diabetics should be focussed on patients with cardiomegaly and previous myocardial infarction. Among patients without either cardiomegaly or previous infarction, the risk of ischemic complications was high only among those patients with prolonged hypotension or both hypertension and hypotension.

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Orthotopic Liver Transplantation with Preservation of the Inferior Vena Cava

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Piggyback orthotopic liver transplantation was performed in 24 patients during a period of 4 months. This represented 19% of the liver transplantations at our institution during that time. The piggyback method of liver insertion compared favorably with the standard operation in terms of patient survival, blood loss, incidence of vascular and biliary complications, and rate of retransplantation. The piggyback operation cannot be used in all cases, but when indicated and feasible its advantages are important enough to warrant its inclusion in the armamentarium of the liver transplant surgeon.

ORTHOTOPIC LIVER TRANSPLANTATION is a well-standardized operation[1,2] in which the inferior vena cava from above the renal veins to the diaphragm is removed as part of the recipient hepatectomy. The excised retrohepatic vena cava is replaced with a donor vena caval segment into which all of the hepatic veins drain. The safety and ease of the operation have been improved by the use of a veno-venous bypass technique that permits the obstructed vena cava as well as the occluded splanchnic venous system to be decompressed during the anhepatic phase.[3]

We report here a piggyback modification of this procedure whereby the full length of the recipient inferior vena cava is preserved. This kind of operation has been performed before,[1-4] but it has not been fully described. A particularly appealing feature of the operation in children for whom veno-venous bypass might not be feasible is that vena caval occlusion can be avoided during the hepatectomy.

Methods

Case Material

We have used the technique intermittently since the late 1960s. However retrieval of all cases in our experience proved to be impractical. For purposes of the present study, only the time between January 1988 through April 1988 was considered; at this time 24 piggyback operations were performed (compared to 103 standard procedures).

The results with the piggyback operation were compared with those in paired controls. The controls consisted of the pediatric or adult case immediately preceding the piggyback procedure (Table 1).

The age of the piggyback recipients ranged from 10 months to 60 years, mean 36 years. In the piggyback group, there were four children who were 10 months to 15 years old (mean, 7.1 years). The adults were 30 to 60 years old (mean, 42.1 years). The control population was almost identical (Table 1).

Surgical Technique

The hilar structures were dissected, ligated, and divided (Fig. 1). In some cases it was possible to rotate the liver out of the wound to dissect the individual hepatic veins (Fig. 2). The small hepatic veins were ligated and divided. The major veins were crossclamped (Fig. 3) because they were used to fashion an orifice for the outflow anastomosis of the homograft suprahepatic vena cava (Figs. 4 and 5). The three principal veins (right, middle, and left) were joined by dividing the intervening septa in 19 cases. The

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TABLE 1. *Comparison of the "Piggyback"* Versus *the Standard Technique*

Variables	PB Ped.	PB Adults	Standard Ped.	Standard Adults
Number of cases	4	20	4	20
Age	7.1	42.1	4.7	43
Intraop. blood loss (UPCs)	5	17	4	17.5
ReTx	1	2	0	4
V–V bypass	3	18	3	20
Hep. artery thrombosis	1	0	0	1
Portal v. thrombosis	0	0	0	2
Biliary stricture	0	3	1	0
Biliary leak	0	0	0	0

left and middle veins were joined in three cases, and the right and middle veins were used in two cases.

If difficulty was encountered in dissecting the hepatic veins, an alternative technique was used in which the liver was split, thereby opening the liver like a book and allowing the hepatic veins to be controlled from inside (Figs. 6 and 7). The principle of intraparenchymal exposure has been described previously for transplantation[5] and for major hepatic resections.[6] A tributary free plane is identified at the upper portion of the liver, and with gentle blunt dissection the finger is burrowed down the anterior surface of the vena cava. The liver is divided down to the finger (Fig. 6). Under direct vision it is then possible to see, ligate, or clamp the hepatic vein branches passing to the vena cava (Fig. 7).

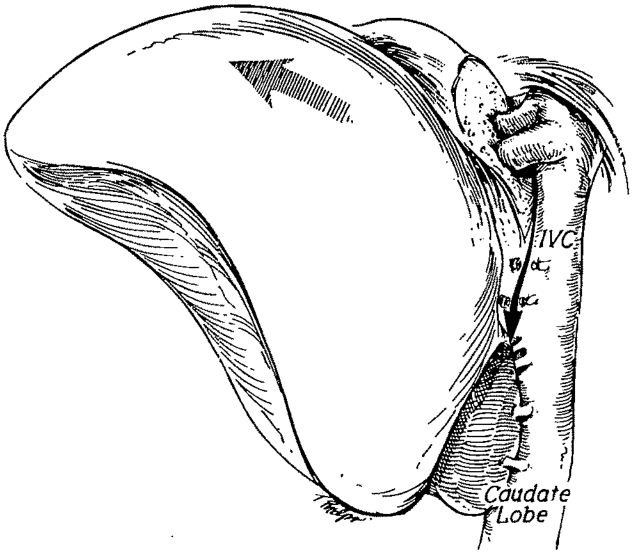

FIG. 2. The left lobe is rotated and individual hepatic veins are ligated. The major hepatic veins are exposed.

The technique of liver insertion is similar to the standard method, except for the outflow anastomosis, which is made to the anterior or anterolateral surface of the host vena cava. The exact location of this anastomosis depends on which of the major hepatic veins have been used. The lower end of the inferior vena cava of the homograft is either ligated or sutured (Fig. 8).

Retransplantation became necessary in three of the 24

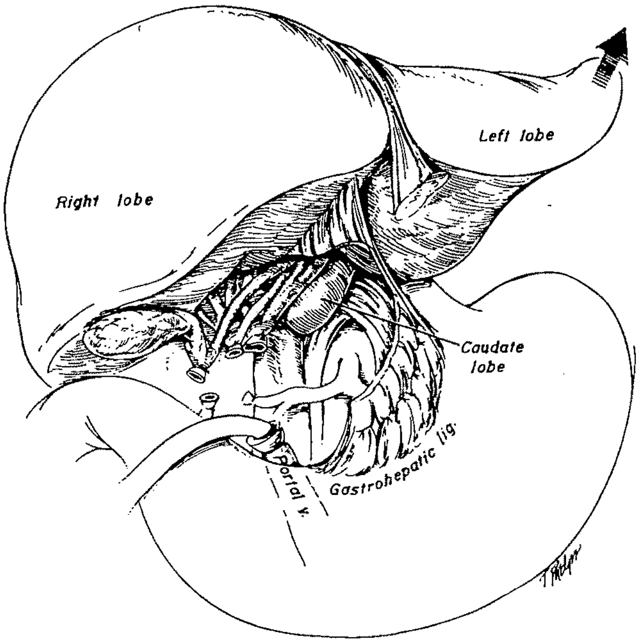

FIG. 1. The hilar structures are dissected, ligated, and divided. The portal vein is cannulated for the veno-venous bypass.

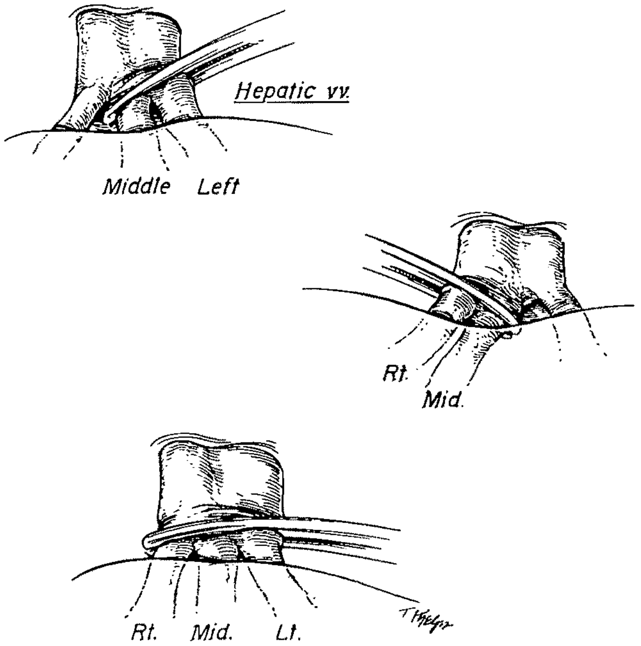

FIG. 3. The major hepatic veins are crossclamped.

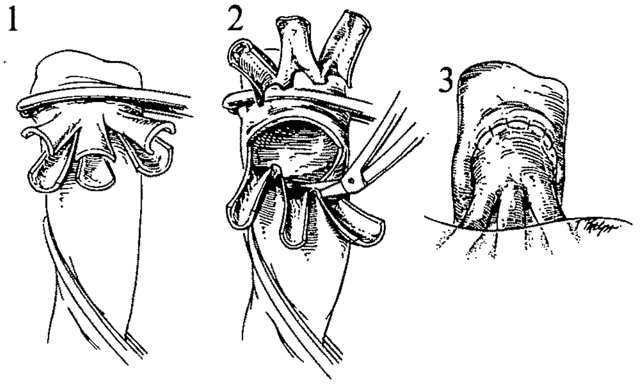

FIG. 4. Cuffs are fashioned for the outflow anastomosis.

recipients of piggyback livers, and the repeat operation was unusually easy because of the ability to reuse the outflow vena cava of the original homograft (Fig. 9).

Veno-venous bypasses of both the vena caval and portal systems were used for all of the adult recipients of the piggyback livers. In the adult patients the cuffs fashioned from the hepatic veins sometimes were prepared in a bloodless field with a clamp below this site. With the children a special attempt was made to maintain flow in the vena cava as dissection of the hepatic veins was taking place and during the anastomosis.

Results

There was a very high rate of success in both the piggyback and control groups with more than 90% of all patients surviving for at least 3 months (Table 1). There was no significant differences between the two groups in blood loss, retransplantation rate, portal vein or hepatic artery thrombosis, or biliary tract complications.

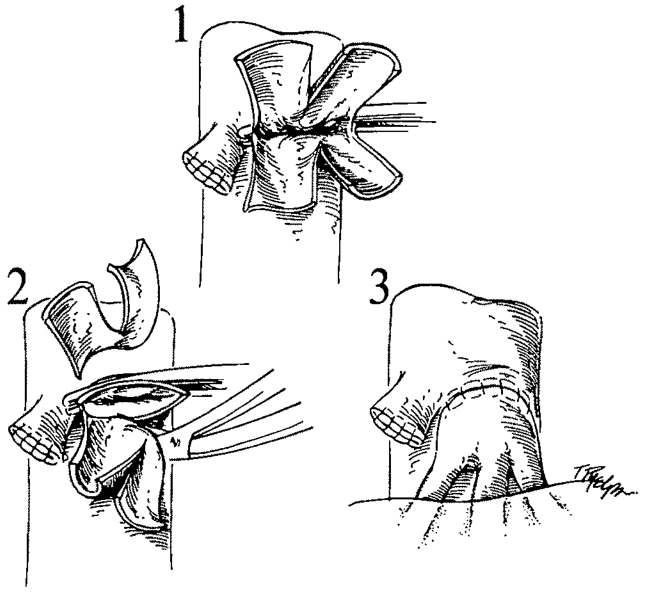

FIG. 5. Cuffs are fashioned for the outflow anastomosis.

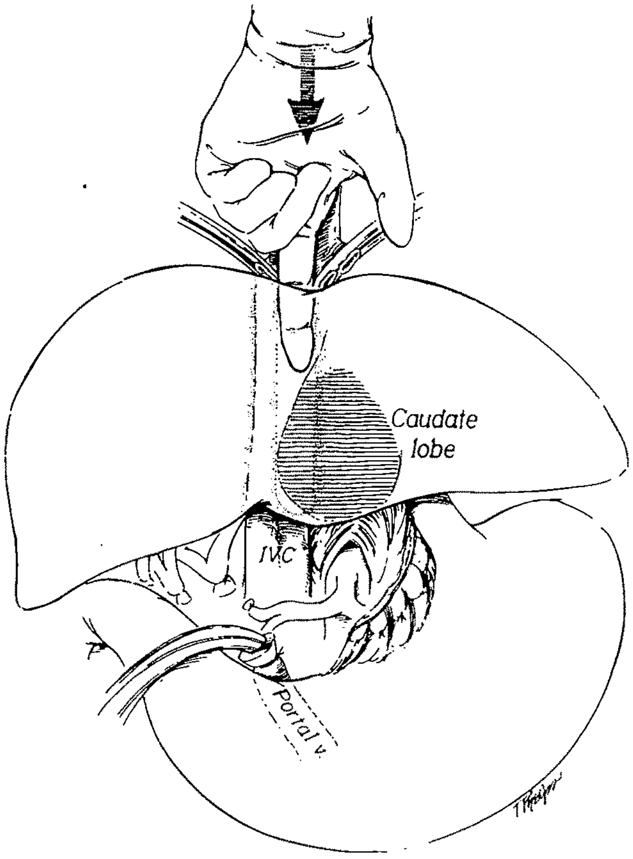

FIG. 6. A plane is developed on the anterior surface of the vena cava.

In one piggyback recipient, a thrombus was identified with ultrasonography 1 week after transplantation in the donor inferior vena caval stump. Anticoagulant therapy was not given. The thrombus could not be identified 1 month later with repeat ultrasonography. There was no evidence of pulmonary embolus in this or any other patient.

Discussion

The use of the piggyback technique depends on finding favorable anatomic conditions as the recipient hepatectomy proceeds. The least favorable circumstances tend to be with small cirrhotic livers, whereas the most favorable are with large livers in diseases such as primary biliary cirrhosis or sclerosing cholangitis in which the large hepatic veins are relatively normal and accessible. Patients with liver malignancies should not be considered because the tumor margin may be jeopardized. Children with biliary atresia have suitable anatomy for the piggyback procedure in at least one half of the cases. The ease of performance is the best guideline in deciding whether to at-

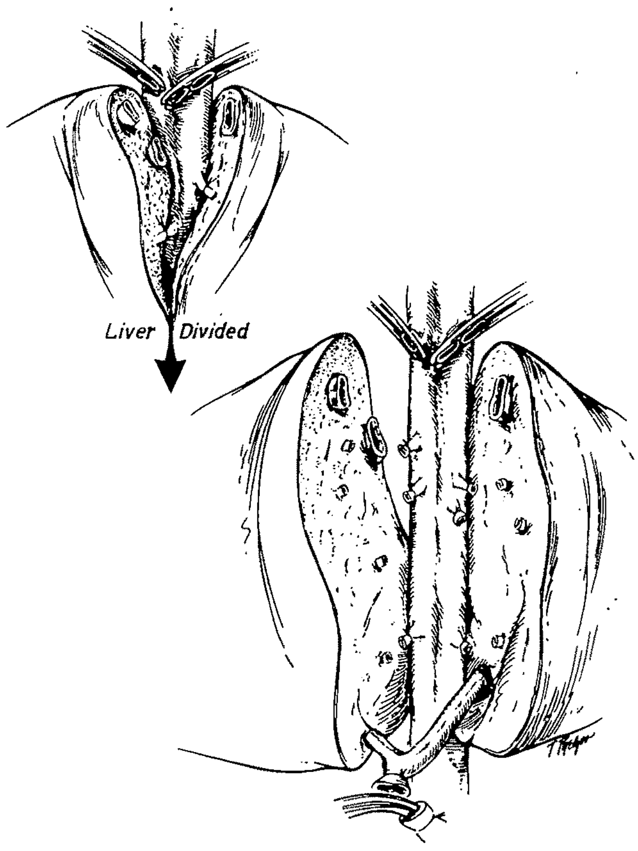

FIG. 7. Intraparenchymal exposure of the hepatic veins.

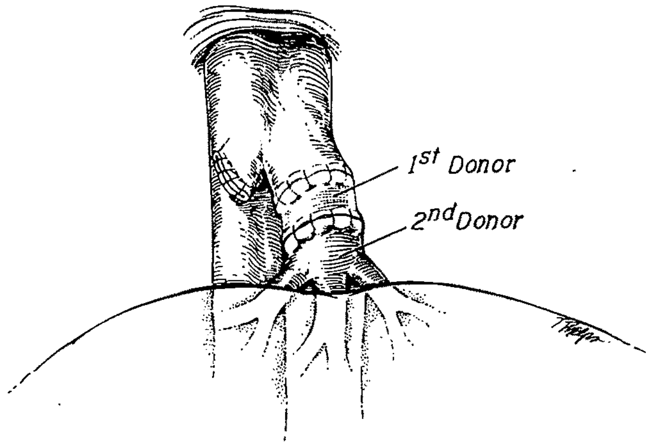

FIG. 9. Retransplantation: a rim of the suprahepatic cava of the original graft is retained.

tempt this operation rather than the standard one. If difficulties are encountered, it is best to abandon the piggyback operation and remove the vena caval segment.

However the piggyback operation has very significant advantages for patients who have suitable anatomy. The physiologic disturbance can be minimized if the vena caval circulation is not occluded in the anhepatic period, especially in children in whom a bypass is not used. In either children or adults, less raw surface is created, thus making subsequent hemostasis easier. The technique of splitting the liver down to the vena cava can be life saving, even if the retrohepatic vena cava is not spared. In some patients the liver may be frozen into the hepatic fossa by previous operations to the extent that it cannot be safely mobilized and removed by any other expedient.

A strong argument for the piggyback operation can be made in only a minority of cases, the 19% incidence during the period of the present study probably being a realistic projection. The piggyback technique may have special value if a liver from a substantially smaller donor is to be transplanted because it may be easier to adjust disparities in length of the donor and recipient vessels. Also for the transplantation of lobar or segmental fragments, the placement of these partial livers with a piggyback technique can provide greater versatility than the standard orthotopic approach can.

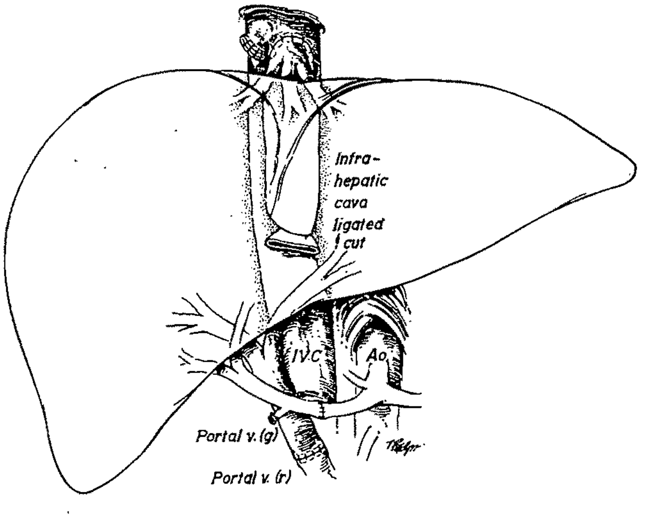

FIG. 8. The final appearance of the graft.

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Natural History of *In Situ* Breast Cancer in a Defined Population

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The entire experience of *in situ* breast cancer in Alberta from 1953 to 1984 was examined. Of 243 patients coded, 226 were available for review by a panel of three pathologists. In 149 cases the diagnosis of *in situ* disease was confirmed. One hundred and eight patients had 109 ductal carcinomas *in situ*, 38 patients had lobular carcinomas *in situ*, with 3 patients having both. A multitude of treatments was used, ranging from local excision to radical mastectomy. Survival at a mean of 6 years follow-up was equal in all groups, with only two patients with a confirmed diagnosis of ductal carcinoma *in situ* dying from clinically suspected systemic disease. In patients treated by local excision, ipsilateral cancers were seen in 12% of ductal carcinoma *in situ* patients who had local excision and 13% of patients with lobular carcinoma *in situ*. Contralateral metachronous invasive cancers were seen in 6% of ductal carcinoma *in situ* patients and 3% of lobular carcinoma *in situ* patients. No lymph node involvement was seen in any of these patients, either with prophylactic dissection or in follow-up. The conclusion reached was that both *in situ* lesions are similar in their clinical course. Lymph node dissection is not necessary. Pathologic review is critical for accurate studies, with a change in diagnosis of 36% of diagnoses. Treatment does not appear to affect prognosis. The most appropriate treatment needs to be determined in prospective randomized trials.

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WITH THE RAPID increase in the frequency of diagnosis of *in situ* breast cancer using screening mammography, we are faced with a treatment philosophy in total disarray. Recommendations for surgical therapy of lobular carcinoma *in situ* (LCIS) and ductal carcinoma *in situ* (DCIS) range from biopsy to modified mastectomy or even bilateral mastectomy with reconstruction.[1] How can we justify more surgery for noninvasive disease than for infiltrating cancer?

Rather than being a reflection of our irrational nature, this therapeutic dilemma results from an inadequate data base of the natural history of *in situ* breast cancer, particularly in intraductal carcinoma.[2] Our apparent confusion also results from concern related to the psychosexual implications of aggressive surgery, which many would identify as prophylactic, possibly unnecessary and disfiguring. To date we have struggled to answer the question with data from retrospective studies at major referral institutions. A natural history study documenting an entire population during an extended period has not been done. For this reason we have taken advantage of a comprehensive cancer registry established in 1953 in Alberta, Canada. All patients with a diagnosis code of *in situ* breast cancer were studied and they form the basis of this analysis.

Methods

All patients coded in the Alberta Cancer Registry between 1953 and 1984 for DCIS or LCIS, with or without microinvasion (MI), were reviewed. Registration of cancer patients has been mandatory since the Registry's inception in 1953 and is considered virtually complete because pathologists' offices submit copies of pathology reports of all malignant diagnosis to the Cancer Registry. The age of the patient, pathologic diagnosis, treatment, recurrence pattern, and survival were evaluated.

All available slides on these patients were reviewed independently by three pathologists. When disagreement existed the final diagnosis was determined by reviewing

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the slides together on a multiple-head microscope and discussing areas of significant disagreement to arrive at a unanimous or majority opinion.

The diagnosis of LCIS was reserved for filling and distension of acinar structures with typical small uniform round cells with round or oval nuclei. The diagnosis of DCIS was based on the findings of any one of the recognized variants, specifically solid, cribriform, micropapillary, or comedo pattern. Major criteria in establishing a diagnosis of DCIS rather than atypical ductal hyperplasia (ADH) in noncomedo carcinoma included a single population of cells with prominence of nuclear chromatin in round or oval nuclei that were uniformly distributed within the cross-sectional ductal area, had punched-out appearing rounded spaces (cribriform or colanderiform), and no streaming of cells.

Results

Two hundred forty-three cases coded as *in situ* breast carcinoma were identified in the Alberta Cancer Registry. Slides from 226 cases were available for review. All pathologists agreed in 80% of the cases and two of three agreed in 20% of the cases. The original coded and final consensus diagnoses are shown in Table 1. The diagnosis was changed for 36% of the patients.

One hundred nine DCIS lesions in 108 patients and 40 LCIS lesions in 38 patients were identified on review, with 3 patients having both DCIS and LCIS lesions, for a total of 143 patients. Of the 138 registry diagnoses of DCIS, 91 were confirmed, 3 were considered to show MI, 5 were invasive ductal carcinoma (DC), and a large group of 39 lesions were categorized on review as florid DH or ADH—borderline lesion.

TABLE 1. In Situ *Breast Cancer in Alberta: Review of Pathology*

Coded Diagnosis	No. of Lesions	Final Diagnosis	No. of Lesions
DCIS	138	DCIS	91
		DCIS/MI	3
		DH/ADH†	39
		DC§	5
DCIS MI	33	DCIS MI	4
		DCIS	16
		LCIS	1
		DH/ADH	6
		DC	6
LCIS	54	LCIS	38
		ALH	12
		DCIS	2
		LC‖	2
LCIS MI	1	LCIS	1

* DCIS, ducal carcinoma, *in situ.*
† LCIS, lobular carcinoma, *in situ.*
‡ DH, ductal hyperplasia; ADH, atypical ductal hyperplasia.
§ DC, infiltrating ductal carcinoma.
‖ LC, infiltrating lobular carcinoma.

TABLE 2. *Bilateral Lesions Associated with 143 Patient* in Situ *Breast Carcinomas*

First Lesion Detected	No. of Lesions	Second Lesion Detected	No. of Lesions
Metachronous			
DCIS*	6	LCIS	1
		DC	5
LCIS†	3	DCIS	2
		DC	1
DC‡	15	DCIS	13
		LCIS	2
LC§	2	LCIS	2
Synchronous			
DCIS/DCIS	1		
LCIS/LCIS	2		
DCIS/DC	4		
DCIS/LC	1		
LCIS/LC	3		

* DCIS, ductal carcinoma, *in situ.*
† LCIS, lobular carcinoma, *in situ.*
‡ DC, infiltrating ductal carcinoma.
§ LC, infiltrating lobular carcinoma.

Thirty-three cases of DC with microinvasion (DCIS MI) were coded as DCIS in the Registry. Review of these revealed 4 cases of DCIS MI, 16 DCIS lesions, 6 DH/ADH cases, and 1 case in which the reviewers considered the lesion as LCIS with extension to terminal ducts. Six lesions showed invasive DC.

Of the 54 cases of LCIS in the Registry, 38 were confirmed and 12 were downgraded to atypical lobular hyperplasia. Two were considered DCIS and two were invasive lobular carcinoma (LC).

Bilateral lesions were found in 37 patients, 11 of them synchronous and 26 metachronous (Table 2).

Thirty-one patients had an invasive carcinoma, either synchronous (8) or metachronous (23), associated with an *in situ* lesion and were excluded from evaluation of follow up. Twenty-three of these invasive carcinomas were associated with DCIS lesions. Eight of the invasive carcinomas were associated with LCIS, leaving a total of 115 *in situ* lesions in 112 individual patients for further study. DCIS was associated with either *in situ* or infiltrating carcinoma in the other breast in 27 patients (25%) and LCIS was similarly associated in 13 patients (33%). Taking into account total follow-up time, bilateral disease incidence rates were 0.04 per person-year in DCIS patients and 0.07 per person-year in LCIS patients. No significant difference ($p > 0.10$) in bilateral disease incidence in the two patient groups was found when confidence intervals were calculated (based on the large sample Normal distribution of the maximum likelihood estimator ln [RateRatio]).[3]

The mean ages of patients with DCIS and LCIS were

TABLE 3. In Situ *Breast Cancer in Alberta 1953–1984*

Age and Follow-up	No. of Patients DCIS 85	 LCIS 30
Age range (years)	30–88	32–78
Mean age (years)	55	50
Mean follow-up (years)	6	6

55 years and 50 years, respectively. The mean follow-up was 6 years for each group (Table 3). Of these, 47 patients with DCIS and 17 patients with LCIS were followed for at least 5 years. Survival rates were 98% and 100%, respectively.

Treatment modalities for these patients are illustrated in Table 4. Local excision was used in 21% of breasts with lesions of LCIS and in 28% of breasts with lesions of DCIS. Subcutaneous mastectomy and/or mastectomy without nodal dissection was used in 43% with LCIS and 26% in DCIS. This included five patients who had contralateral subcutaneous mastectomies in four cases for LCIS and one case for DCIS. Fifty-three per cent of patients with DCIS and 33% of patients with LCIS had mastectomies with associated axillary dissection of varying levels. This included 3% in each category who had radical mastectomies. Of the 17 of 109 DCIS lesions that had local excision, two patients had local recurrence: one was DCIS with MI and the other was infiltrative cancer, resulting in an incidence of 12% (Table 5). In the 7 of 40 LCIS lesions that were treated by local excision, two had recurrence of LCIS, and one an invasive tubular carcinoma in the ipsilateral breast.

No regional nodal involvement was found with either *in situ* lesion. This was the case both in patients having lymphadenectomy done prophylactically or in clinical assessment of the undissected axilla at follow-up. In two patients with a diagnosis of DCIS, systemic cancer was subsequently diagnosed clinically. One patient died 8 years after diagnosis without autopsy to confirm the clinical suspicion that the primary cause of death was breast cancer. The other patient is alive after 7 years without biopsy confirmation.

TABLE 4. *Treatment of 118* in Situ *Breast Cancer Lesions in Alberta from 1953–1984*

Surgical Procedure	No. of Lesions (%) DCIS	 LCIS
Local excision	17 (28)	7 (21)
Subcutaneous mastectomy	3 (3)	6 (18)
Mastectomy	20 (23)	8 (25)
Mastectomy + L1 nodes	14 (16)	7 (21)
Mastectomy + L1, L2, L3 nodes	29 (34)	3 (9)
Radical mastectomy	3 (3)	1 (3)

TABLE 5. *Follow-up of 118* in Situ *Breast Cancers in Alberta from 1953–1984*

Disease Site	No. of Lesions (%) DCIS	 LCIS
Local recurrence	2/17 (12)	3/7 (43)
Regional involvement	0/86 (0)	0/32 (0)
Systemic recurrence	2/85 (2)	0/32 (0)
Subsequent contralateral metachronous carcinoma	5/85 (6)	1/30 (3)

Eighty-five patients with DCIS had 86 lesions; 30 patients with LCIS had 32 lesions.

Subsequent contralateral metachronous invasive lesions were noted in 6% of the patients who had a diagnosis of DCIS and in 3% of patients with a diagnosis of LCIS.

Discussion

This report provides as accurate an assessment as possible of *in situ* breast cancer. There is no similar report. It avoids selection bias by using the entire population of Alberta to document the natural history of the disease. In contrast other types of retrospective studies, and to some extent even prospective studies, include unwanted factors such as patient selection by pattern of practice associated within or outside an institution.

The pathologic criteria for DCIS and LCIS have changed over the years and guidelines are still far from precise. The pathologic review of all original slides is a key factor in this study. Diagnosis of *in situ* disease was altered in 34% of the patients. Among the three review pathologists, a minor difference of opinion existed in 20% of the cases, the major difficulty residing in the atypical hyperplasia/borderline carcinoma *in situ* group. Variations in diagnosis arose because of difference in opinion as to whether spaces were truly colanderiform or fenestrated; whether the cell population was truly of a uniform type; how major the criterion of necrosis was; how much reviewers were influenced by minor criteria; and how significant nuclear atypia was. Minor difficulty was also encountered in defining what constituted MI. Before invasion was diagnosed, the presence of irregular single cell infiltration was required. Lesions showing lobular extension with an adjacent lymphoid reaction and fibrosis were considered *in situ* lesions with alteration in the specialized stroma of the lobular unit rather than invasion accompanied by a lymphoid and fibroblastic response. For LCIS, variation in diagnosis among the three pathologists occurred relative to the number of involved acini required for diagnosis and the nature of small spaces in these areas—real or artifact and intra- or intercellular. It is therefore critical that in any retrospective or prospective study of this disease that the pathology be reviewed by an expert pathologist or, preferably, a team of experts, as was done in this report. Because surgeons are generally not aware of the difficulty in making this diagnosis, it is important that quoted data have this key requirement before accepting any study as a valid analysis of this disease.

The treatment strategies reported in this group of patients reflect the confusion felt by all clinicians. However central to any clinical decision must be the consideration of the possible effects of treatment on the ultimate survival of these patients.[4] Because the survival of patients in our series of DCIS and LCIS *in situ* lesions was 98% and 100%, respectively, no appreciable survival benefit can be attributed to any therapeutic approach. This low mortality rate is reported in other studies as well.[4] In this disease the advantages of treatment must, therefore, be restricted to the considerations of long-term preservation of the breast anatomy and the possible psychological problems associated with the identification of the high risk of development of new premalignant and malignant lesions in either breast, which is indeed a significant event.[5,6]

LCIS was associated with a new lesion in the ipsilateral breast in three of seven patients (43%) who had local excision and with a contralateral *in situ* or invasive lesion in 34% of the total group. Only one of the lesions in either side was a metachronous infiltrative cancer. These findings that either breast is at significant risk for a subsequent infiltrating cancer has been reported previously, both in series in which routine contralateral mirror-image biopsies have been done and with long-term follow-up.[5-7]

The incidence of associated lesions with DCIS was similar to LCIS ($p > 0.20$).[3] Only 12% of patients with local excision had microinvasive ipsilateral recurrence. However during this time 6% of patients also had contralateral invasive lesions and an overall association of bilateral lesions in 26 of the 109 patients, for an incidence of 24%. This latter observation casts an entirely different light on the problem of local recurrence. Rather than always being secondary to disease left behind, which progresses into an infiltrating lesion, it suggests that new lesions in the ipsilateral breast may be due to the unstable epithelium throughout. This concept is supported by Holland[8] who, using the Egan whole mount method of sectioning the ipsilateral breast, found that 40% of lesions had diffuse or multifocal involvement over a 5-cm diameter, despite the fact that 75% were nonpalpable. Lagios[9] also noted that an index lesion larger than 2.5 cm had an associated multicentric involvement throughout the entire breast of 54%. These pathologic findings appear to be clinically relevant in that four studies report that 25% to 30% of patients who have one breast removed for DCIS have an identified second lesion in the opposite breast when removed either prophylactically or therapeutically in follow-up.[4] Thus it would appear that the DCIS lesion behaves in a very similar fashion to the LCIS lesion.

This observation is in marked contrast to the previously held concept that DCIS is an ipsilateral disease.[4,10-14] However this conclusion has also been suggested by others in the past.[15] With our understanding of infiltrating breast cancers—a multicentric disease that is both infiltrating and noninfiltrating—it is rational and not surprising to find that the two premalignant lesions behave in a similar manner. Biologically, therefore, one would predict that the progression of the neoplastic change in the breast range from atypical hyperplasia through *in situ* carcinoma of either type to infiltrating cancer.[16,17] The progression to this invasive form may take years to develop. In this series of patients there was no significant association with either the side or the histology of the index lesion because the initial diagnosis of *in situ* disease and the subsequent lesion histologically did not correlate.

Evaluation of current treatment is best done in the trial setting. Outside this methodology, the issues become relative. The value of a mastectomy to avoid all local recurrence or development of unilateral infiltrating disease has been shown for the ipsilateral breast in a retrospective report by Sunshine and others.[2,4] This approach was associated with long-term survival rates of close to 100%. Prospective trials now suggest that at 5 years local recurrence of an infiltrative lesion is 5% or less with local excision and radiotherapy.[13,18,19] Lagios has also shown that after a wide local excision there is only 5% recurrence locally.[9] Whether treatment with a total mastectomy, coupled with the subsequent cosmetic consequences and problems associated with reconstruction, is equal or better to a breast conservation procedure, subject to a 5%-to-10% incidence of ipsilateral recurrent cancer, is best answered in close consultation between patient and physician. A young woman with this disease will possibly opt for a far different treatment than an older woman would. Factors such as the patient's desires and wishes, family situation, and family support will also play a very important part when there appears to be no survival differences in the short term. The risk for a second lesion is as high in the opposite breast. Therefore rather than it being a decision to choose either local excision or a total mastectomy, the decision must be between a bilateral total mastectomy with reconstruction or local excision. This consideration is appropriate in both lesions.

Lymph node involvement has not been considered a feature of LCIS. However early reports suggest that it is at least 5% in DCIS patients.[10] Our study showed no lymph node involvement either at the time of prophylactic lymph node dissection or in clinical follow-up of the undissected axilla. Recent series report the incidence now in no more than 1% of patients.[13,18] This does not support the inclusion of lymph node dissection in the management of this disease.[13,18,20]

No patients with LCIS developed systemic disease. However two patients with DCIS who did not develop a subsequent associated infiltrating DC had metastatic disease diagnosed clinically without documentation of the pathology. If, in fact, these were from the original DCIS, this phenomenon could be explained by undetected synchronous infiltrating lesions associated with DCIS.[9,21]

Conclusions

The strengths of these observations are based on a population-based analysis supported by a current review of the pathologic diagnosis. The natural history of this disease in this population suggests that *in situ* breast cancer is associated with a continuum of neoplastic changes of the breast ranging from atypical hyperplasia to *in situ* carcinoma and infiltrating carcinoma. Because no treatment modality influenced survival, the observations within the context of a median follow-up of 6 years is believed to reflect the natural history, despite the retrospective methodology. The most striking finding is the propensity of not only LCIS but also DCIS to be associated with bilateral lesions of either *in situ* or infiltrating carcinoma. Differences between DCIS and LCIS are more quantitative than qualitative, with DCIS having only slightly less incidence of bilateral disease. Lymph node involvement is not a feature of either disease. The treatment dilemma may be largely resolved with prospective studies. In the meantime it would appear that the appropriate controversy in either disease would hinge around a local excision, possibly with radiotherapy *versus* a bilateral prophylactic mastectomy with reconstruction. Obviously the patient, the patient's family, and the physician play critical roles in this decision and the ultimate management.

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False Aneurysms After Prosthetic Reconstructions for Aortoiliac Obstructive Disease

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Several aspects of false aneurysm development after prosthetic reconstruction for aortoiliac obstructive disease were studied. For this purpose the long-term results (up to 20 years of follow-up) of 518 patients with implanted arterial prostheses in the aortoiliofemoral tract were retrospectively evaluated. Completeness of follow-up data was 83.2% 15 years after operation. A total of 101 false aneurysms (21 aortic, 53 iliac, and 27 femoral) were detected in 69 patients and verified by operation. The incidence per patient was 69 of 518 patients (13.3%). The incidences per anastomosis were: aortic, 21 of 438 anastomoses (4.8%); iliac, 53 of 835 anastomoses (6.3%); and femoral, 27 of 198 anastomoses (13.6%). Almost one half (47.5%) of all the false aneurysms were asymptomatic and were detected by angiography or ultrasonography. Chances for late survivors to develop a false aneurysm during follow-up were calculated by the life-table method. The chance to be free of a false aneurysm at any site was 77.2% 15 years after operation. These chances were 92.3%, 84.5%, and 76.2% for aortic, iliac, and femoral anastomoses, respectively. Analyses of subgroups showed that the development of a false aneurysm was significantly correlated with the presence of hypertension, multilevel disease, the type of suture material, and the type of anastomosis. These results indicate unexpectedly high chances for the development of false aneurysms in long-term survivors after aortoiliac or aortofemoral prosthetic reconstructions. We advocate the use of a life-long follow-up schedule with periodic angiography and ultrasonography for these patients.

AN ANASTOMOTIC OR FALSE aneurysm after prosthetic vascular reconstruction is usually considered a rare late complication. However information as to its exact incidence is not readily available because it has been reported to vary from 0.5% to 23.7%,[1,2] depending on the type of procedure, the location of the anastomosis, the type of prosthesis, the type of suture material, and the length of follow-up. Information regarding the chance, with time, for developing a false aneurysm after prosthetic reconstruction is not available because cumulative incidence rates (calculated according to the standard actuarial method of life-table construction) are absent in the literature.

The present retrospective study evaluates all patients subjected to vascular prosthetic reconstruction for aortoiliac obstructive disease (AIOD) at our institution between 1958 and 1980 to determine the cumulative incidence rate and thus the chance for developing a false aneurysm during a follow-up period of two decades. In addition this study includes the evaluation of several risk factors that may be associated with the occurrence of false aneurysms.

Material and Methods

Clinical Material

This study evaluates all patients at risk for the development of a false aneurysm after prosthetic reconstruction for AIOD performed at our institution from 1958 through 1980. Therefore only patients surviving the surgical procedure were included. Their number is 518, of whom 471 (90.9%) were men and 47 (9.1%) were women. Their median age at the time of operation was 55.9 years. In 500 patients it was the first aortoiliac reconstructive procedure; in 18 patients an endarterectomy of various aortoiliac segments had been performed in an earlier stage. A history of hypertension (diastolic pressure of more than 100 mm Hg) was present in 157 patients (30.5%), and 37 (7.2%) had diabetes mellitus. The indication for operation was based on the combination of physical and angiographic findings in all cases. Of all 518 patients, 398 (76.8%) were claudicators, while 73 (14.1%) suffered from rest pain and

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47 (9.1%) had nonhealing foot ulcers or gangrene. As judged by angiography, there were 237 patients (45.8%) with single-level disease (obstructive lesions restricted to the aortoiliac tract) and 281 patients (54.2%) with multilevel disease (obstructive lesions in both the aortoiliac tract and the arteries of the leg).

Surgical Procedures

The variety of surgical procedures applied is listed in Table 1. Insertion of an aorto-bi-iliac prosthesis was the most common form of treatment in 331 of 518 cases (63.9%). Whenever feasable extension of the prosthesis beyond the inguinal ligament was avoided to minimize the presence of groin wounds with underlying prostheses and their associated risks.[3] Proximal anastomoses with the aorta were preferentially end-to-end (403 of 437 cases, 92.2%) and were routinely reinforced with a prosthetic cuff of one-size-increased-bore diameter. In 34 of 437 (7.8%) cases the proximal anastomosis with the aorta was made in an end-to-side fashion. Distal anastomoses were also preferentially end-to-end (iliac, 573 of 835 anastomoses, 68.6%; femoral, 101 of 198 anastomoses, 51%), unless circulation of the hypogastric arteries could be maintained by end-to-side distal anastomoses (iliac, 256 of 835 anastomoses, 30.7%; and femoral, 95 of 198 anastomoses, 48%). The types of 1 aortic, 6 iliac, and 2 femoral anastomoses were not retrievable in retrospect examination.

From 1958 through 1963, a total of 33 teflon and 51 dacron prostheses were implanted, while two denatured homografts were used in that period. As of 1964 we have always inserted double velours knitted dacron prostheses.

Anastomoses and arteriotomies were closed with running sutures. Before 1966 we used silk sutures, but from 1967 through 1976 we used braided dacron (Tevdek^R, Deknatel, Floral Park, NY) sutures for all anastomoses. Starting in 1977 the use of monofilamentous suture material (Prolene^R, Ethicon, Nordestedt, FRG) became progressively more common, initially for the iliac and femoral anastomoses (almost exclusively from 1978) but later also for the anastomoses with the aorta.

Unless contraindicated after operation, all patients were give oral anticoagulants (Coumadin, DuPont Laboratories, Wilmington, DE) that were continued in principle for a patient's lifetime.

Methods of Follow-up and Completeness of the Number of Patients in Study During Follow-up

Patients were routinely seen at 3, 6, 12, and 24 months after operation and then at 2-year intervals for the rest of their lives. The condition of the vascular reconstructions was, in the early years, determined by physical examination, while in the later years noninvasive studies were also performed (segmental pressure indices). Starting in 1978 ultrasound studies were routinely performed to check all prosthesis-to-artery anastomoses. Angiography was also performed when ultrasound studies were of poor quality, when serious complications were expected, or when a reoperation was considered. Suspicion of a false aneurysm was usually considered an indication for reoperation.

The present study includes follow-up data up to December 31, 1984. Follow-up data of an individual patient were considered complete when this patient had fulfilled the routine follow-up schedule until death or December 31, 1984. We could judge the completeness of individual follow-up data because definitive information on late deaths could be retrieved from the local municipal administrations for all but seven patients, of whom information regarding their survival was not retrievable because they had left the country. Of the other 511 patients, 119 (23%) had not completely fulfilled the routine follow-up schedule. They entered the analysis according to their clinical status when last seen and were considered lost to follow-up for the remaining period until their individual deaths. Because these 119 patients became lost to follow-up after various periods of having fulfilled the regular follow-up schedule, we believed it to be relevant to calculate the completeness of follow-up data of the entire group at various postoperative intervals. This was performed by calculating the number of patients in the study—thus still fulfilling their routine follow-up schedule—at various postoperative intervals and the number of all patients alive at the same time. The quotient of these figures reflects the completeness of follow-up data at the end of the chosen time interval. The completeness of follow-up data is presented in Figure 1. The number of patients in the study was 369 (*i.e.*, 72.2% of the original population with exclusion of the 7 emigrated patients), 200 (39%), 84 (16.4%),

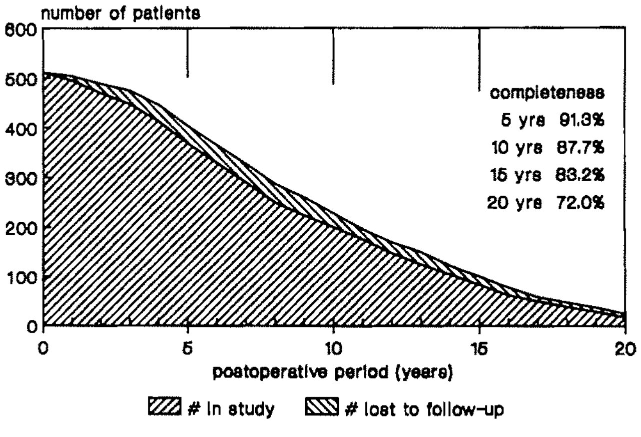

FIG. 1. Number of patients actually evaluated at varying periods of postoperative follow-up and number of patients lost to follow-up at the same times. Completeness of follow-up was calculated as the quotient of the number of patients in study and the number of patients alive (patients in study plus patients lost to follow-up) at the same postoperative time.

and 18 (3.5%) 5, 10, 15, and 20 years after operation, respectively. The completeness of follow-up data was 91.3%, 87.8%, 83.2%, and 72% at these 5-, 10-, 15-, and 20-year intervals, respectively. The number of patients available for evaluation 20 years after operation was considered too small from which to draw valid conclusions. Our conclusions are therefore based on the 15-year results.

Data Management, Calculations, and Statistical Procedures

All clinical data were stored in a computerized vascular registry. We used the SPSS-X program, installed in a mainframe computer, which provided data base facilities and multiple options for statistical analysis. Individual data items were checked for validity. Checks included numeric ranges, code selections, and so on. Consistency checking was performed on groups of data items that were known to be mutually dependent, *e.g.*, progression of dates of birth, operation, discharge, follow-up visits, and death.

The incidence of false aneurysms was calculated in two ways. First the incidence per patient was calculated as the quotient of detected false aneurysms—only the first detected false aneurysm was taken into account—and the total number of patients with implanted prostheses. However this figure by no means reflects the chance of a patient to develop a false aneurysm because this calculation does not include length of follow-up or mortality. The same holds for the calculation of the incidence per anastomosis. Therefore the incidence was also calculated in a second fashion, cumulative absence rate of false aneurysms (CARFA), and was calculated according to the standard actuarial method of life-table construction,[4] censored by mortality, and lost to follow-up. These CARFA figures reflect a patient's chance to develop a false aneurysm at various postoperative intervals. This was done for the entire group and for various subsets of the population to determine the effect of several risk factors, such as location of the anastomosis, hypertension, multi-level disease, type of suture material, and so on. For the calculation of the CARFAs for aortic anastomoses, only the patients with aortic proximal anastomoses were included (n = 437). The same criterion was used for the calculation of the CARFAs for iliac (n = 473) and femoral (n = 155) anastomoses. In patients with two femoral or two iliac false aneurysms, only the first detected false aneurysm was taken into account.

Comparison of the survival curves of subgroups was performed by using the Lee-Desu test statistic.

Results

Incidence of False Aneurysms

When related to the number of patients, the incidence of false aneurysms was 13.3% because 69 of the 518 patients revealed at least one false aneurysm. All but four false aneurysms were proved to be present at operation because two patients refused operation and in two other patients operation was not advised. The interval between insertion of the prosthesis and detection of the (first) false aneurysm varied from 1 to 238 months, with a median interval of 92 months and a regular spread. The chance for a patient to develop a false aneurysm is graphically illustrated in Figure 2, the curve of which represents the cumulative absence of false aneurysms over the total observation period of 20 years in all 518 patients with aortoiliac prostheses (the first detected aneurysm at whatever location was taken into account). The CARFAs were

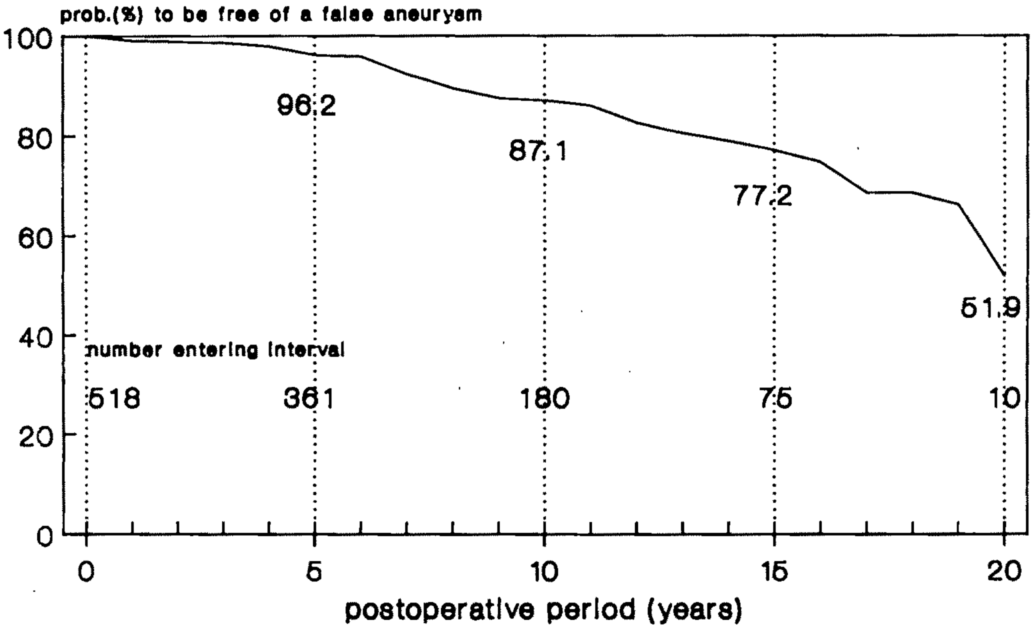

FIG. 2. Cumulative absence of false aneurysms at any location (aortic, iliac, or femoral) in all 518 patients with prosthetic reconstructions for AIOD.

TABLE 1. *Types of Reconstruction in all 518 Patients and Number of Anastomoses at Aortic, Iliac, and Femoral Sites*

Type of Prosthesis*	No. of Patients	%	Anastomoses Aortic No.	 Iliac No.	 Femoral No.
Bifurcated prostheses					
AI_2	331	63.9	331	662	–
AF_2	43	8.3	43	–	86
AI_1F_1	59	11.4	59	59	59
Tube prostheses					
AA	1	0.2	2	–	–
AF	1	0.2	1	–	–
IF	52	10.0	–	52	52
AI	2	0.4	2	2	–
II	29†	5.6	–	60	–
	518	100.0	438‡	835§	198‖

* AI_2, aortobiliac bifurcated prostheses. AF_2, aortobifemoral bifurcated prosthesis. AI_1F_1, one side aortoiliac, other side aortofemoral bifurcated prosthesis. AA, AF, IF, AI and II, aortic, aortofemoral, iliofemoral, aortoiliac, and ilioiliac tube prosthesis, respectively.

† In one patient a bilateral ilioiliac tube prosthesis was inserted.

‡ Four hundred thirty-seven patients with a total of 438 aortic anastomoses, of which 403 end-to-end, 34 end-to-side, and type of anastomosis were not retrievable in one case.

§ Four hundred seventy-three patients with a total of 835 iliac anastomoses, of which 573 end-to-end, 256 end-to-side, and type of anastomosis were not retrievable in 6 cases.

‖ One hundred fifty-five patients with a total of 198 femoral anastomoses, of which 101 end-to-end, 95 end-to-side, and type of anastomosis were not retrievable in 2 cases.

96.2%, 87.1%, 77.2%, and 51.9% at 5, 10, 15, and 20 years, respectively.

We also have calculated the incidence of false aneurysms per anastomotic location. Therefore all double and triple false aneurysms had to be taken into account. More than one false aneurysm was encountered in 25 (36.2%) of all 69 patients with false aneurysms, of whom 18 had two false aneurysms and seven had three false aneurysms at different locations. In 19 cases these false aneurysms were found simultaneously and in six cases they were found at different postoperative intervals. Recurrence of false aneurysms (*i.e.*, at the same location) is not included in these calculations and was found in six patients. Thus, when excluding the recurrent aneurysms, 44 patients had false aneurysms at 1 site, 18 patients had false aneurysms at 2 different sites, and 7 patients had false aneurysms at 3 different sites. So a total of 101 (44+36+21) false aneurysms at different anastomotic sites were encountered: 21 aortic, 53 iliac, and 27 femoral aneurysms. Because the total number of aortic, iliac, and femoral anastomoses was 438, 835, and 198, respectively (Table 1), the incidence of false aneurysms per aortic, iliac, and femoral anastomosis was 4.8%, 6.3%, and 13.6%, respectively.

Figure 3 shows the cumulative absence of false aneurysms at the aortic, iliac, and femoral sites over the total observation period of 20 years (only the first detected false aneurysm per location was taken into account). The respective CARFAs at 5, 10, 15, and 20 years were 99%, 95.3%, 92.3%, and 71.6% for aortic anastomoses, 98%, 92.5%, 84.5%, and 60.2% for iliac anastomoses, and 95.5%, 83.9%, 76.2%, and 61.8% for femoral anastomoses.

Techniques for the Detection of False Aneurysms

The 101 false aneurysms observed in 69 patients were detected during follow-up in several ways. Only 36 (35.7%)

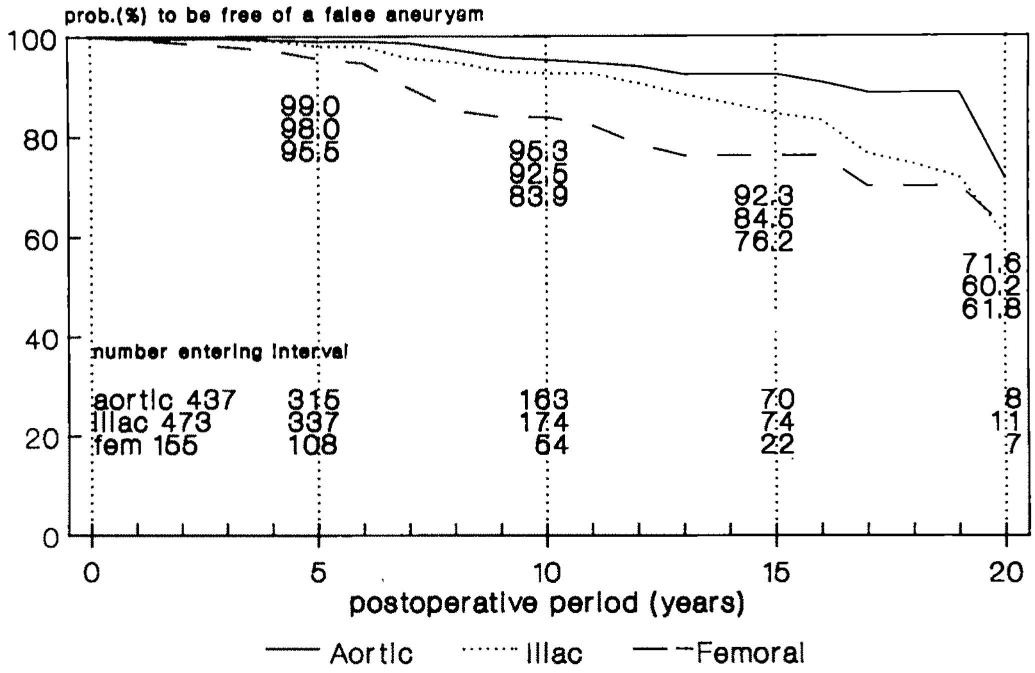

FIG. 3. Cumulative absence of false aneurysms at specific locations in three subgroups: (1) 437 patients with 438 aortic anastomoses, (2) 473 patients with 835 iliac anastomoses, and (3) 155 patients with 198 femoral anastomoses.

false aneurysms were found by physical examination. Complications like rupture or formation of an anastomotic-enteric or anastomotic-ureteric fistula, necessitating an emergency operation, were the presenting symptoms of 17 false aneurysms (16.8%). The remaining 48 (47.5%) false aneurysms were asymptomatic and hidden from detection at physical examination. Of these 48 false aneurysms, 47 were detected by ultrasonographic studies made routinely in our follow-up schedule or by angiographic studies carried out for various reasons, and one was found coincidentally at postmortem examination. Figure 4 shows how the false aneurysms were detected according to the site of occurrence. Of the 21 aortic false aneurysms, only 2 (9.6%) were found by physical examination, 14 (66.7%) by angiography or ultrasound studies, and 5 (23.8%) were discovered because of complications such as rupture (2) and fistula formation (3). Of the 53 iliac false aneurysms, 11 (20.8%) were found by physical examination, 30 (56.6%) by angiography or ultrasound studies, 11 (20.8%) because of complications (7 ruptures and 4 fistulas), and one (1.9%) was found coincidentally at postmortem examination. The majority of the 27 femoral false aneurysms (23, *i.e.*, 85.2%) was found by physical examination, while only 3 (11.1%) were discovered by angiography and one (3.7%) had ruptured.

Patient-Associated Risk Factors

We have considered two conditions as patient-associated risk factors for the development of false aneurysms. One was a history of hypertension and the other was the presence of multi-level disease as a possible indicator of severe arteriosclerotic involvement. Their influence was separately analyzed using the life tables based on the occurrence of the first false aneurysm at any site. Results for hypertension are presented in Figure 5. The CARFAs at 5, 10, 15 and 20 years were 94.7%, 78.7%, 68.5%, and 71.4% for patients with hypertension and 96.8%, 90.8%, 81%, and 61.5% for patients without hypertension, indicating a statistically significant difference (p value = 0.01) in favor of the latter patients. Results for multi-level disease are presented in Figure 6. The CARFAs were 94.2%, 83.4%, 74.6%, and 48.7% for patients with multi-level disease and 98.2%, 90.9%, 79.9%, and 54.6% for patients with single-level disease, indicating a small but statistically significant difference (p value = 0.03) in favor of the latter patients.

Procedure-Associated Risk Factors

We have investigated the effect on false aneurysm development of three procedure-associated risk factors: the type of prosthetic material, the type of suture material, and the type of anastomosis (end-to-end or end-to-side). Results are given in Table 2.

For investigating the influence of prosthetic material only, patients operated on before 1964 were included because this is the only period during which both types of prostheses (teflon and dacron) were used. By this restriction the influence of period-associated parameters such

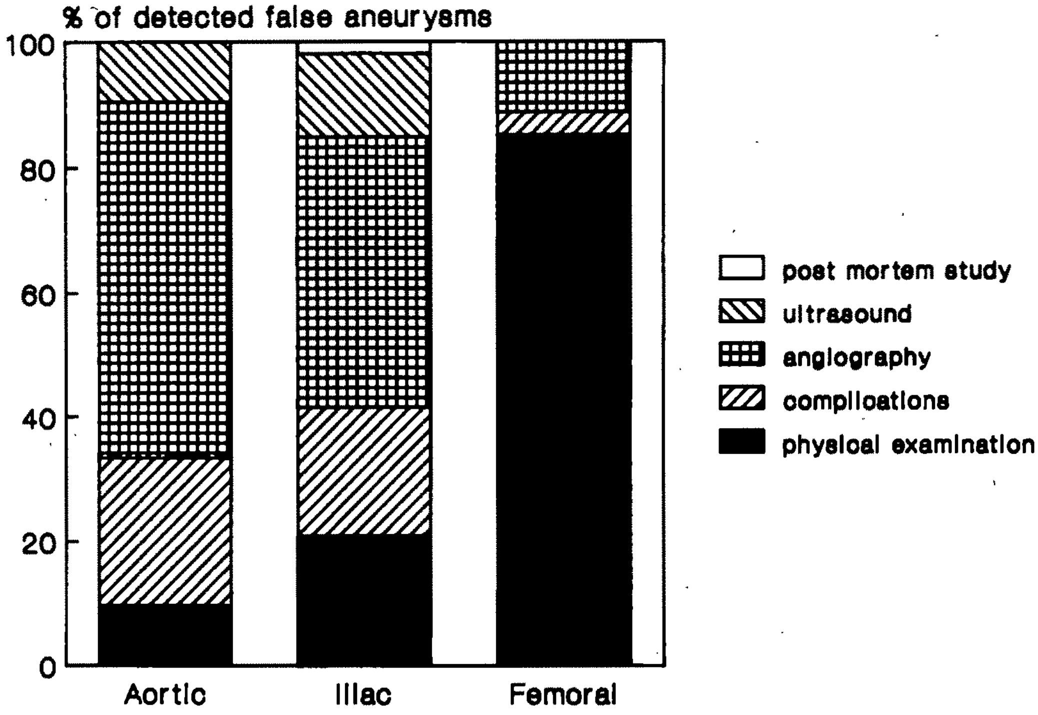

FIG. 4. Contribution of several ways of clinical presentation to the detection of false aneurysms at specific locations.

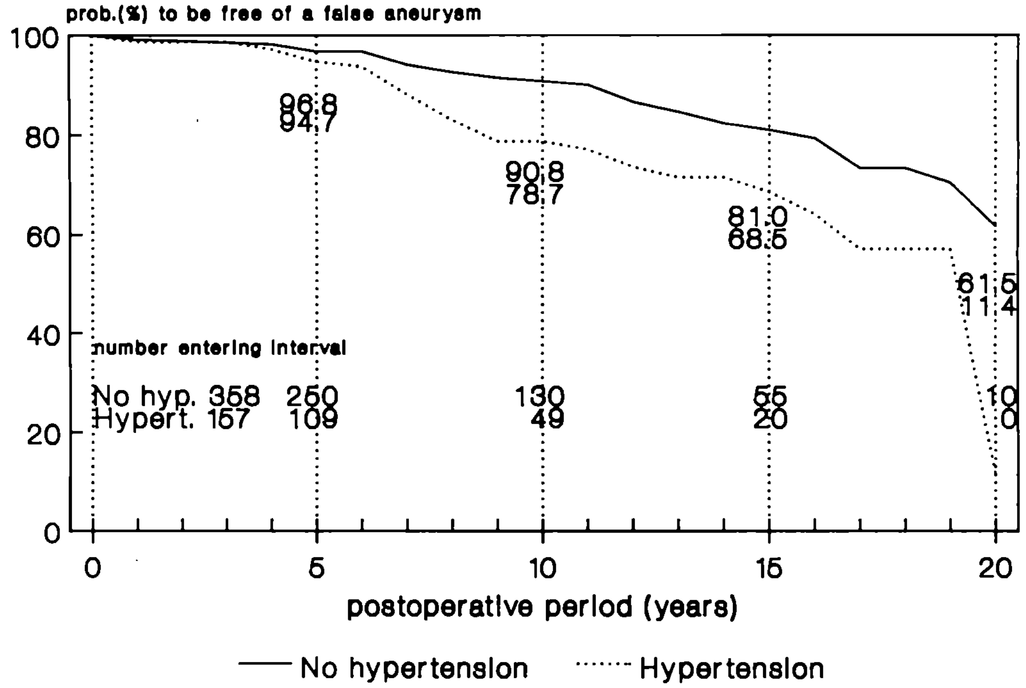

FIG. 5. Comparison of cumulative absence of false aneurysms at any location in patients with and without hypertension. The differences are statistically significant (p = 0.01).

as the type of suture material was excluded. Life tables based on the first false aneurysm at any site were used and we found no influence of the type of prosthetic material on the chance to develop a false aneurysm (p value = 0.68).

The influence of the type of suture material and of the type of anastomosis was analyzed using the life tables based on the occurrence of false aneurysms at specific sites. Therefore aortic, iliac, and femoral anastomoses were analyzed separately. In regard to the influence of suture material, it should be noted that intraoperative assessment of the false aneurysms showed silk sutures to be fragmented and therefore the most likely cause of anastomotic disruption. In contrast false aneurysms of anastomoses made with synthetic suture material (braided dacron) had developed despite persisting integrity of the sutures, while

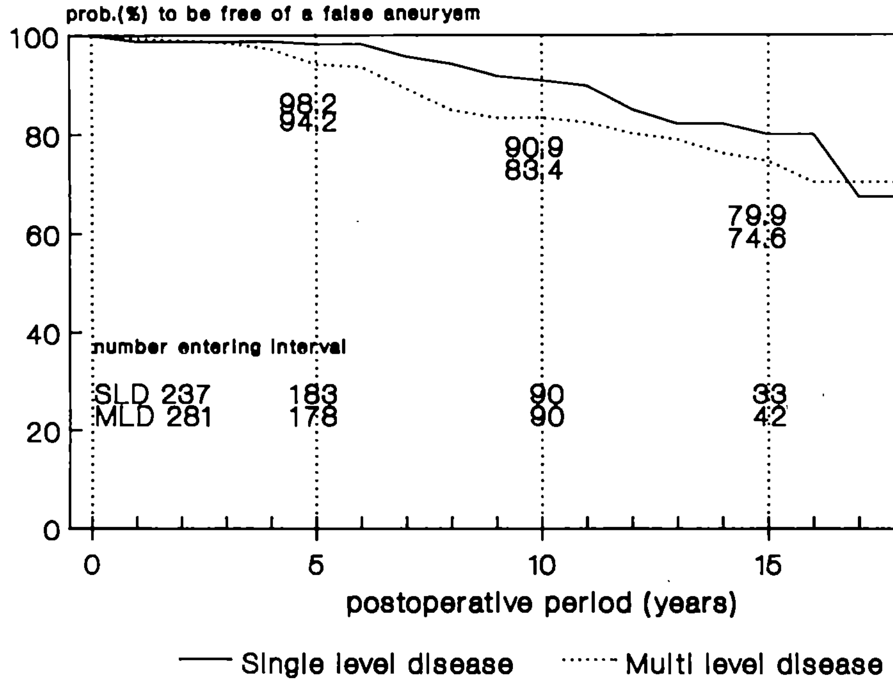

FIG. 6. Comparison of cumulative absence of false aneurysms at any location in patients with single-level disease and patients with multilevel disease. The differences are statistically significant (p = 0.03).

TABLE 2. *Effect of Procedure-Associated Risk Factors on the Cumulative Absence Rate of False Aneurysms at Various Postoperative Intervals*

		Cumulative Absence Rates (%)				
Risk Factor	No. of Patients	5 Years	10 Years	15 Years	20 Years	p Value*
All anastomoses†						
Dacron	51	95.6	89.5	71.5	71.5	
Teflon	33	89.1	81.0	75.8	66.3	0.68
Aortic anastomoses						
Silk suture	128	98.3	91.2	86.8	68.0	
Tevdek suture	287	99.2	97.4	96.2	—	0.03
End-to-end	403	99.2	97.5	94.9	79.8	
End-to-side	34	96.6	75.9	70.7	0	<0.001
Iliac anastomoses						
Silk suture	140	95.7	87.0	79.8	57.9	
Tevdek suture	225	98.5	95.7	84.4	—	0.01
Prolene suture	87	100.0	—	—	—	
End-to-end	275	98.7	94.3	85.8	70.7	
End-to-side	120	97.0	90.7	83.3	47.5	0.15
Femoral anastomoses						
Silk suture	52	93.6	79.4	68.4	55.3	
Tevdek suture	79	97.1	88.6	83.5	—	0.47
Prolene suture	17	92.3	—	—	—	
End-to-end	80	96.9	89.0	85.5	85.5	
End-to-side	60	92.3	78.2	65.5	42.4	0.24

* p values based on the Lee-Desu test statistic, comparing survival curves.

† Only patients operated on before 1964.

the prosthesis appeared to be torn out of the host artery, suggesting weakness of the arterial wall as the principal cause of false aneurysm development.

At all sites, silk sutures were associated with a higher incidence of false aneurysms, as compared to braided dacron (Tevdek^R) sutures. P values for aortic, iliac, and femoral anastomoses were 0.03, 0.01, and 0.47, respectively. Monofilament polypropylene (Prolene^R) sutures were only used at the end of the observation period, which caused the number of patients in the study to be too small from which to draw valid conclusions.

Regarding the influence of the type of anastomosis, we found that at all sites end-to-side anastomoses were associated with a higher incidence of false aneurysms than were end-to-end anastomoses. However the difference was statistically significant for aortic anastomoses ($p < 0.001$) but not for iliac ($p = 0.15$) or femoral anastomoses ($p = 0.24$).

Discussion

The Incidence of False Aneurysms

Reported incidences of false aneurysms vary widely from 0.5% to 23.7%.[1-3,5-12] To explain these wide variations, several factors should be considered.

First the reported series show major differences regarding the types of arterial reconstruction under study. Endarterectomies and autologous graft procedures may have been included, although it is generally agreed that the occurrence of false aneurysms is largely limited to the use of synthetic prostheses.[3] The location of the anastomoses is often not taken into account, although femoral anastomoses bear the greatest risk of developing a false aneurysm.[2,3,5] Moreover false aneurysms with simultaneous infections at these locations are sometimes excluded,[6,10] whereas they should be included whenever there is a reason to believe that the false aneurysm preceded the infection. Obviously differences in selection criteria may be associated with substantial differences in the observed incidence of false aneurysms.

Second there are major differences in the length and completeness of follow-up. Because false aneurysms can develop at any postoperative interval,[6,8,13] their incidence will increase with the length of the postoperative observation period, and a substantial number of false aneurysms may easily remain undetected when many patients are lost to follow-up.

Finally there is the matter of the technique used for the detection of the false aneurysms because many of them are hidden from detection by physical examination. The routine use of ultrasound studies or angiographies during follow-up may safely be taken to reduce the number of undetected false aneurysms and, therefore, reported incidences are influenced by the techniques applied during follow-up.

These considerations imply that a reliable comparison of various series is extremely difficult if not impossible. The same holds for comparing the absolute incidence of

13.3% as found in our series with the incidences reported by others and even for comparing this result with the incidences reported by Szilagyi et al.[11] and Crawford et al.,[12] although their studies had a comparable length of follow-up.

It should be emphasized that these absolute incidences, calculated as the quotient of detected false aneurysms and the number of primary operations, do not reflect the patient's chance to develop a false aneurysm because the calculation of these absolute incidences does not include death or the length and completeness of follow-up. From the clinical point of view it seems more appropriate to express the incidences as CARFAs censored by mortality and lost to follow-up. These rates do indicate the chances of a patient to be free of a false aneurysm at a certain postoperative interval, provided that the patient survives this interval. We found CARFAs of 96.2%, 87.1%, 77.2%, and 51.9% at 5, 10, 15, and 20 years, respectively, indicating unexpectedly high chances to develop a false aneurysm in the long term after prosthetic vascular reconstruction. We cannot compare these results with those of others because studies with a similar approach have not yet been published.

Methods of Detecting False Aneurysms and the Problem of Hidden False Aneurysms

False aneurysms can quite easily be hidden from detection by physical examination. This holds especially for aortic and iliac locations, as reflected by the fact that we detected our aortic and iliac false aneurysms largely by angiographic and ultrasound studies (Fig. 4). But also the femoral false aneurysms, especially the small ones in obese patients, can be missed by physical examination (11.1% in our series). That false aneurysms often remain undetected by physical examination can also be deduced from several other reports, in which these false aneurysms were coincidentally detected when angiography was performed for a coexisting, physically apparent, false aneurysm at another location.[7–10,14,15] Hidden false aneurysms can remain hidden because they do not necessarily increase in size or lead to complications.[3]

Predictably the routine use of periodic ultrasound scans and angiography, as suggested by several authors,[5,13] will decrease the number of undetected false aneurysms. However it should be kept in mind that false-negative investigations do occur not only in our experience but also in the experience of Lee et al.,[16] who found that ultrasonography was only 50% accurate in patients with aortic prostheses when an aneurysm was suspected. In addition some false aneurysms in our series were detected by ultrasonography, but could not be visualized by angiography due to partial thrombosis of the false aneurysm. Therefore any method of calculating the incidences of false aneurysms will inevitably underestimate the real incidence of false aneurysms.

Etiologic Factors Associated with the Occurrence of a False Aneurysm

Although multiple factors probably are present in most patients, certain single events may play a principal role in the pathogenesis of false aneurysms. We have separated patient-associated risk factors and procedure-associated risk factors because the former probably cannot be influenced and the latter can.

Patient-Associated Risk Factors

We believe, as do many others, that the quality of the vessel wall[3,6,7,10,13] and the compliant mismatch of the host artery and prosthesis[13,17] are the most important factors in the development of a false aneurysm. In our experience, too, most false aneurysms had developed in spite of the integrity of the suture material. In addition the remarkably high incidence of double or triple false aneurysms as found by us (36.2%) and many others[7–10,14,15] suggests the existence of an undetermined patient factor that leads to the development of false aneurysms. We found a lower absence rate of false aneurysms in patients with multi-level disease as compared to patients with single-level disease (Fig. 6), suggesting that the severity of arteriosclerotic disease, as measured by the extension of arteriosclerotic lesions, is related to the quality and compliance of the vessel wall. In our series a history of hypertension significantly decreased the absence rates of false aneurysms (Fig. 5). Other authors,[1,3,13] too, have mentioned hypertension as a factor of considerable importance.

Procedure-Associated Risk Factors

Considering the incidence of false aneurysms at specific locations, we found the highest incidence at the femoral site (Fig. 3). Although femoral anastomoses bear the highest risk of developing a false aneurysm,[2,3,9,18] the aortobifemoral prosthetic reconstruction remained first choice in the treatment of aortoiliac occlusive disease for many surgeons.[19–21] The increased complexity of the aorto-biiliac procedure, with its concomitant risks,[3] as well as the greater need for reoperation due to recurrent disease in the external iliac and femoral segments,[19,20,22] has been argued to outweigh the risk of false aneurysm development at femoral anastomoses. The remarkably high chance of false aneurysm development that we found makes it worthwhile to reconsider the preferential type of reconstruction.

The type of prosthetic material can be a factor in the pathogenesis of false aneurysms due to fraying, compliant mismatch, or dilatation.[3,13,17,23–25] We compared the results of teflon and dacron prostheses and found no significant difference (Table 2).

In our series false aneurysms developed significantly more often when silk sutures had been used as compared to braided dacron sutures (Table 2). The etiologic role of the type of suture material in the pathogenesis of false aneurysms has been discussed by many authors.[26–28] Polypropylene monofilamentous sutures were used in a number of patients that was too small and for a period that was too short to permit reliable conclusions.

The efficacy of end-to-end anastomoses, as compared to end-to-side anastomoses, in providing the most suitable hemodynamic conditions for the prevention of false aneurysms has been described by several authors.[23,29,30] We also found a trend in favor of end-to-end anastomoses, although the differences were statistically significant only for the aortic anastomoses (Table 2).

We conclude that the incidence of false aneurysms in patients with aortoiliac prosthetic reconstruction is unexpectedly high and that its principal etiologic factor—weakness of the arterial wall—cannot be influenced. Moreover an unknown number of these false aneurysms will remain undetected during follow-up. The occurrence of false aneurysms can probably be reduced by using synthetic suture material for the anastomoses and by making the anastomoses in an end-to-end fashion. Because femoral anastomoses bear the greatest risk of developing false aneurysms, the preference of the aortobifemoral prosthetic reconstruction in the treatment of aortoiliac occlusive disease should be reconsidered. Finally patients with prosthetic arterial reconstructions should be included in a life-long follow-up schedule with periodic ultrasonic and angiographic studies.

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Studies in Fetal Wound Healing

IV. Hyaluronic Acid-Stimulating Activity Distinguishes Fetal Wound Fluid from Adult Wound Fluid

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Recent clinical and experimental evidence suggests that the fetus responds to injury in a fashion fundamentally different from that of the adult. Our initial experience with human open fetal surgery reinforces experimental observations that the fetal wounds heal without the scarring, inflammation, and contraction that often accompany adult wounds. In this study we examine fetal wound fluid in an attempt to elucidate the control mechanisms that endow the fetus with unique healing properties. The extracellular matrix of fetal wounds is rich in hyaluronic acid, a glycosaminoglycan found in high concentrations whenever there is tissue proliferation, regeneration, and repair. We establish that wound fluid from the fetus contains high levels of hyaluronic acid-stimulating activity that may underlie the elevated deposition of hyaluronic acid in the fetal wound matrix. In contrast there was no hyaluronic acid-stimulating activity present in adult wound fluid. Hyaluronic acid, in turn, fosters an extracellular environment permissive for cell motility and proliferation that may account for the unique properties observed in fetal wound healing.

THE ERA OF OPEN fetal surgery has arrived. Experience at the Fetal Treatment Program (University of California, San Francisco) with this new surgical frontier includes twelve human fetuses, from 18 to 27 weeks gestation.[1] This clinical experience reinforces experimental observations in various animal models that the fetus responds to injury in a fashion fundamentally different from that of the adult.[2–10] Fetal wounds heal rapidly and without the scarring, inflammation, and contraction that often accompany adult wound healing.

These unique qualities of fetal wound healing may be attributed to a unique extracellular matrix (ECM). The fetal matrix has an entirely different profile of macromolecular structural constituents compared to the adult ECM. The fetal ECM is richer in glycosaminoglycans, particularly hyaluronic acid (HA).[9,10] The purpose of this study was to define the mechanisms by which HA is deposited in such abundance in the fetal wound and to compare that process with adult wound healing.

HA is found in high concentration whenever tissue proliferation and regeneration occur.[11] It is involved in the detachment process of the cell cycle that allows cells to move.[12] A burst of HA synthesis occurs before mitosis so that the dividing cells become dissociated from neighboring cells.[13–16] HA also inhibits cell differentiation, creating an environment that instead promotes cell proliferation.[17,18] HA is composed of alternating units of glucuronic acid and N-acetylglucosamine, and has a key role in the structure and organization of some ECMs that have been well studied, such as cartilage.[19]

We have previously described an HA-stimulating activity in both fetal bovine and sheep serum that has the ability to stimulate the synthesis of HA in a consistent manner.[20] We now establish that fetal wound fluid uniquely contains high levels of HA-stimulating activity, which results in elevated HA synthesis and sustained HA deposition in fetal wounds. We postulate that HA is laid down early in the ECM of both fetal and adult wounds, but HA deposition remains elevated for an extended time period only in fetal wounds. This may provide a permissive environment for healing through regeneration and growth, rather than through scarring and fibrosis.

Materials and Methods

Wound Cylinders

Sterile wire mesh cylinders were used as described by Schilling and Hunt.[21,22] The cylinders were made by cut-

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ting a rectangle from No. 40 mesh, 36-gauge stainless steel, rolling them into a tube and folding the ends closed. The fetal cylinders measured 1×3 cm, and the adult cylinders were 3×6 cm (Fig. 1).

Fetal Wound Fluid

Time-dated pregnant ewes (Torrel Farms, Ukiah, CA) at 100 days gestation underwent general halothane/oxygen anesthesia using techniques for fetal lamb surgery as previously described.[23] The ewe was prepped and draped sterilely, and a midline laparotomy was made. Using a GIA stapler a hysterotomy exposed the fetal lamb. A 1-cm incision was made in the right axillary crease where excess skin folds were observed. A small subcutaneous pocket was created by blunt dissection, and a single wire mesh wound cylinder was placed in the pocket (Fig. 2). The wound was closed in one layer using interrupted 4-0 silk sutures.

The fetus was returned to the uterus and amniotic fluid volume was restored with sterile normal saline. The hysterotomy was closed, including the membranes, with a TA-90 stapler. The laparotomy was closed in layers, and the ewe was returned to her stall.

Subcutaneous wound cylinders were placed in seven fetal lambs. A separate lamb was used for each time point of wound fluid harvest. The fetal wound fluid was harvested from the wound cylinders (one wound cylinder per animal) by a single percutaneous aspiration under sterile technique during reoperation using an 18-gauge needle and 12-cc syringe on days 1, 2, 4, 6, 8, 10, and 14 after implantation. The fluid was frozen immediately and stored at −70 C until analysis.

Adult Wound Fluid

One nonpregnant adult sheep underwent halothane/oxygen general anesthesia, the large wound cylinders were placed in separate subcutaneous pockets, and the wound was closed with interrupted 2-0 silk sutures. The adult wound fluid was harvested at the same time points as was the fetal fluid by aspirating the wound cylinders using sterile technique. The fluid was frozen at −70 C until analysis.

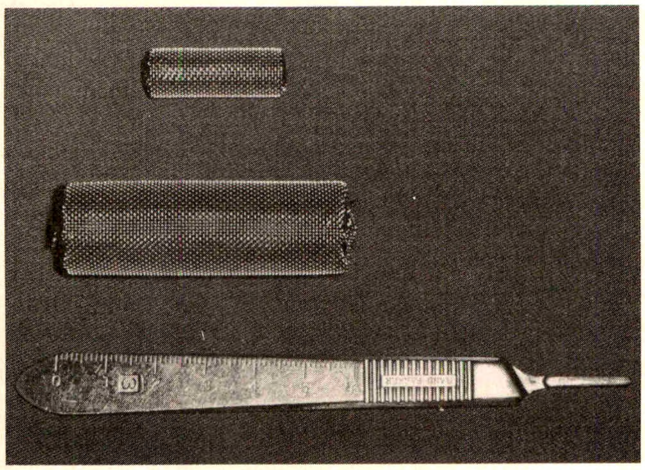

FIG. 1. Photograph of wire mesh wound cylinders. Top: fetal cylinder. Bottom: adult cylinder.

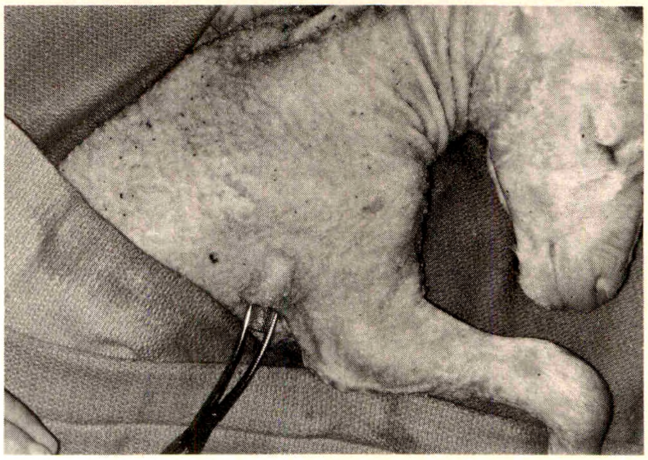

FIG. 2. Photograph of a wire mesh wound cylinder being placed into the right axillary subcutaneous pocket of a 100-day fetal lamb.

Cells and Cell Culture

Rat fibrosarcoma cells were obtained from the laboratory of Dr. Merton Bernfield (Stanford University) and were derived from a methylcholanthrene-treated rat.[24] Such cells have been demonstrated previously to synthesize copious quantities of HA.[25] These cells were cultured in Roswell Park Memorial Institute-1640 (Gibco, Grand Island, NY) with 10% fetal calf serum, 25 mM HEPES (Gibco), 1% penicillin, streptomycin, and Fungizone (Squibb, Princeton, NJ), at 37 C in an atmosphere of 5% CO_2 and 95% air.

Measure of HA Synthesis

Rat fibrosarcoma cells were seeded routinely at a density of 2.5×10^5 cells in wells of 35-mm diameter (Costar, Cambridge, MA). Cells were 50% confluent at this density. Experiments were conducted during the logarithmic stage of growth and were generally concluded when cells were approximately 90% confluent. Cells were allowed to attach for 24 hours and the media was removed, the cells washed three times with low glucose serum-free Dulbecco's modification of minimal essential media H16 (DME H-16, Gibco), and replaced with 1.5 cc of DME H-16 containing 0.1% glucose, 5% calf serum, 1% penicillin, streptomycin, and 25 μg/mL of ascorbic acid. Next 150 μL of the sample to be tested (fetal or adult wound fluid) was introduced, and 1 hour later (^{3}H)glucosamine (44.8 Ci/mmol, New

England Nuclear Corporation) was added for 24 hours. The media, which contains 80% of the synthesized HA, was decanted. The cell layer was then washed with 1 mL calcium-and-magnesium-free phosphate-buffered saline.

To liberate glycosaminoglycans into the solution, proteins, including proteoglycan core proteins, were digested with 5 mg/mL pronase (type XIV bacterial protease, Sigma Chemical, St. Louis, MO), which was freshly prepared each time in 0.2M Tris (Schwartz/Mann), 0.02% Na azide, pH 8.0, and predigested at 37 C for 1 hour. The protease digestion was terminated by boiling the samples for ten minutes. The specific hyaluronidase from the mold *Streptomyces hyalurolyticus* (Calbiochem, La Jolla, CA) was used to digest HA for 2 hours. This enzymatic digestion was also terminated by boiling for ten minutes. The digested solution was precipitated with 7.5% cetylpyridinum chloride (CPC, Sigma Chemical) in the presence of carrier HA and chondroitin sulfate (type A, Sigma Chemical) and transferred onto GF/A glass fiber filters (Whatman, Maidstone, England) using a ten-well vacuum-assisted manifold suction apparatus (Hoefer Scientific, San Francisco, CA). The precipitate on the filter was washed with a 1.5% CPC solution, placed into scintillation vials, and allowed to dry in a 55 C oven. Optifluor^R (Packard, Downers Grove, IL) was then added and the filters were soaked for 24 hours before determination of levels of radioactive label in a Beckman LS 7500 counter (Beckman Instruments, Palo Alto, CA). The level of HA was derived from the difference in radiolabeling in triplicate samples digested in the presence and absence of the hyaluronidase enzyme.

Cell Counts

The duplicate cultures for cell counts were initiated at the same time and grown under conditions identical to their radiolabeled counterparts. A solution of 0.05% trypsin and 0.02% EDTA was used and cells were incubated for one minute to lift cells from the culture dishes. After dilution cells were counted in duplicate using a hemocytometer.

Statistical Analysis

Data are expressed as the mean value for the three samples at each experimental point. The standard deviation is given in each case.

Results

Indicator Cells

As previously reported, the rat fibrosarcoma cells have been established as valid indicator cells for the presence of the HA-stimulating activity.[20] These cells can synthesize large quantities of HA and respond to the serum factor in a time- and dose-dependent manner (unpublished observations). They require 5% calf serum to maintain viability during the assay period. The controls represent culture plates in which no wound fluid was added.

Adult Wound Fluid

Wound fluid obtained by sterile needle aspiration of the subcutaneously placed wound cylinders at 1, 2, 4, 6, 8, 10, and 14 days after implantation was assayed for HA-stimulating activity. Because wound fluid is known to possess mitogenic effects, all activity was expressed on a per-cell basis. At each time point assayed, the adult wound fluid had less HA-stimulating activity than did control samples (Fig. 3). In general the activity decreased, with time reaching its lowest level at 14 days, which was the last point at which a determination was made.

Fetal Wound Fluid

Fetal wound fluid was obtained also by sterile needle aspiration of the wound cylinders at 1, 2, 4, 6, 8, 10, and 14 days after implantation. The assay for HA-stimulating activity was performed, and as with the adult wound fluid, all activity was expressed on a per-cell basis. In sharp contrast to the adult fluid, levels of fetal wound fluid HA-stimulating activity were much higher than adult speci-

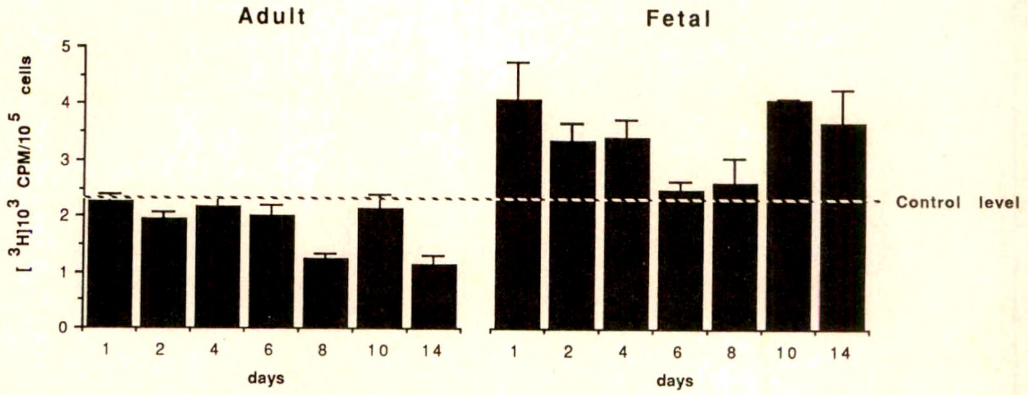

FIG. 3. HA-stimulating activity of adult *versus* fetal wound fluid. The activity was expressed on a per-cell basis as 10^3 radioactive counts per minute per 10^5 cells. As mentioned in Materials Methods, 150 μL of wound fluid was used with the indicator fibrosarcoma cells. The control value represents culture plates in which no wound fluid was added. Error bars represent the standard deviation of each value run in triplicate.

mens at each data point. The HA-stimulating activity appears to be bimodal with apparent maximum activity at days 1 and 10 of harvest.

Mitogenesis

We compared the mitogenic effect of fetal and adult wound fluid on these same indicator cells. As shown in Table 1, adult wound fluid had an increasing mitogenic effect with an apparent maximum at eight days. However by 14 days the fluid has an inhibitory mitogenic effect when compared to the control. By contrast the fetal wound fluid, surprisingly, was not mitogenic above control levels at any of the time points examined (Table 2).

Discussion

The fetus responds to injury in a fashion fundamentally different from that of the adult: the process of mesenchymal proliferation proceeds in the absence of an inflammatory process and fibrosis.[2-10] However the mechanisms that control these differences are unknown and are the objective of our ongoing studies.[20,26,27]

Krummel and DePalma[9,10] demonstrated that the ECM of fetal wounds is rich in glycosaminoglycans, specifically HA. This macromolecule is a key structural and functional component of the ECM, found whenever there is rapid tissue proliferation, regeneration, and repair. It inhibits cell differentiation, creating a permissive environment that promotes cell proliferation.[17,18] We postulate that HA is laid down early in the ECM of both fetal and adult wounds, but that sustained deposition of HA distinguishes fetal from adult wound healing. Our purpose was to determine if fetal wound fluid had the ability to stimulate and sustain HA synthesis. A prolonged presence of HA in fetal wounds may provide the mesenchymal signal for healing by regeneration rather than by scarring and fibrosis. A newly developed *in vitro* assay was used to evaluate HA synthesis in this study based on glycosaminoglycan precipitation with the detergent CPC, measuring the difference of radiolabeled precipitate in the presence and absence of specific hyaluronidase digestion. Siliconized glass fiber filters were used to catch precipitates, so that multiple samples could be assessed simultaneously, unlike other HA assays.[28,29] We used our assay to examine the observations of Krummel and DePalma and to elucidate possible underlying mechanisms.

TABLE 1. *Mitogenic Effect of Adult Wound Fluid*

Sample	Cell Count (10^5 cells)
Control	5.68
1 day	5.50
2 days	6.11
4 days	6.54
6 days	6.66
8 days	7.64
10 days	6.18
14 days	4.85

TABLE 2. *Mitogenic Effect of Fetal Found Fluid*

Sample	Cell Count (10^5 cells)
Control	5.68
1 day	3.77
2 days	4.42
4 days	4.82
6 days	4.64
8 days	4.50
10 days	3.40
14 days	4.00

We used the wire mesh wound cylinder model first described by Shilling and used extensively by Hunt.[21,22] These cylinders have relatively large mesh pores and separate the tissue, creating a dead space that fills with wound fluid. We harvested the wound fluid over a period of 14 days. Previous work has demonstrated that the fetus heals quickly and that sampling fluid from 1 to 14 days would suffice for the evaluation of early and late fetal wound healing.

We chose the fetal lamb because of our extensive experience with this model. We have performed more than 1000 fetal lamb operations in the past decade and have refined a reliable procedure to expose and operate on the fetal lamb.[23] Survival is approximately 90% with such procedures. In addition the long gestation (145 days) allows us to compare fetal wound healing at different gestational ages. This may be crucial because previous work in rats suggests that a spectrum of wound healing exists as a function of gestational age, with wound healing becoming more like that of adult sheep late in gestation.[30]

Our data demonstrate that the levels of HA-stimulating activity between fetal and adult wound fluid differ dramatically. The fetal wound fluid HA-stimulating activity was elevated at each data point. This may underlie the rich deposition of HA in the ECM of fetal wounds. The activity of fetal wound fluid has a bimodal distribution (Fig. 3). One explanation may be that the first peak (days 1 to 4) reflects elevated HA-stimulating activity from fetal sera. The second peak (days 8 to 14), may represent local production of HA-stimulating activity factor by fibroblasts under the influence of trophic factors such as TGF_{beta} contained in wound fluid. In contrast the level of activity in adult wound fluid was below control even at the earliest time point (one day). In general this relatively low level increased as the time points progressed, reaching a maximum at 14 days.

We have also compared the mitogenic effect of fetal and adult wound fluids at each data point. Adult wound fluid was initially mitogenic, but then decreased to below control levels by 14 days. This may be explained by the increased acidity of the adult wound environment between 10 and 15 days.[21] In contrast fetal wound fluid had an inhibitory effect on mitogenesis at all data points. Studies are in progress to measure fetal wound pH and lactate levels.

HA is deposited briefly at the earliest stages of adult wound healing.[31] We have previously demonstrated that the HA-stimulating activity of adult sheep serum is much lower than that of fetal lamb serum. Therefore it is unlikely that a circulating HA-stimulating activity is the basis for the early deposition of HA in the adult wound. A more localized mechanism may be required. Fibrinogen has been shown to contain an HA-binding site. HA may be brought to the wound site by fibrinogen from the circulation, as well as by the fibrinogen contained in alpha granules in platelets.[32-35] In the adult wound, local deposition of HA by the platelet plug and the fibrin clot obviates the need for an exogenous mechanism for stimulating local HA production. We have demonstrated that an HA-stimulating activity is present in the fetal wound for a prolonged period, a mechanism that is entirely absent in the adult wound. Our findings suggest that the mechanism for eliciting the early HA-rich response in adult wounds is entirely different from the prolonged HA-rich response in fetal wounds.

We have previously reported a glycoprotein factor present in fetal sera that stimulates HA synthesis with peak levels of activity occurring at mid-gestation.[20] Thus the HA-stimulating activity (HASA) present in fetal wound fluid may be a reflection of the relative amounts of HASA in fetal sera compared to adult sera. We have also found that fetal urine and amniotic fluid have elevated HA-stimulating activity[20] (Longaker et al., unpublished observations). Unlike fetal sera, the peak activity of amniotic fluid occurs at or near term.[20] This probably reflects the increased contribution of fetal urine to amniotic fluid volume in the second half of gestation. This may be an additional mechanism by which HA is deposited in the matrix of fetal skin wounds because the wounds are bathed in amniotic fluid that contains both an HASA and HA.[36] We are now investigating the effect of excluding fetal wounds from amniotic fluid.

We have also wondered if this HA-stimulating activity crosses the placenta. It turns out that the pregnant ewes have only a slightly higher level of activity than the non-pregnant ewes, which is minimal.[20] In addition we have examined the activity of pregnant maternal urine and have found evidence for a distinct inhibitory activity (Longaker et al., unpublished observations). We are now investigating this phenomenon that may be a protective mechanism for the pregnant ewe.

This study is the first to attempt to analyze constituents of fetal wound fluid and is part of our ongoing effort to investigate the control mechanisms that endow the fetus with unique healing properties.[20,26,27] The ultimate aim of these studies is to apply some of the special features of fetal wound healing to modulate adult wound processes and to avoid fibrosis and contracture.

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Only one H_2 antagonist controls pH for up to 12 hours on a single dose

PEPCID® I.V. (Famotidine, MSD) is indicated in some hospitalized patients with pathological hypersecretory conditions or intractable ulcers or as an alternative to the oral dosage forms for short-term use in patients who are unable to take oral medication.

The recommended dosage is 20 mg q12h. Dosing intervals may need to be prolonged or dosage reduced in patients with severe renal insufficiency (creatinine clearance <10 mL/min) to adjust for the longer elimination half-life of famotidine. All formulations of PEPCID are contraindicated in patients who are hypersensitive to any component of these products. The adverse reactions reported for Tablets PEPCID may also occur with PEPCID I.V. In addition, transient irritation at the injection site has been observed with PEPCID I.V.

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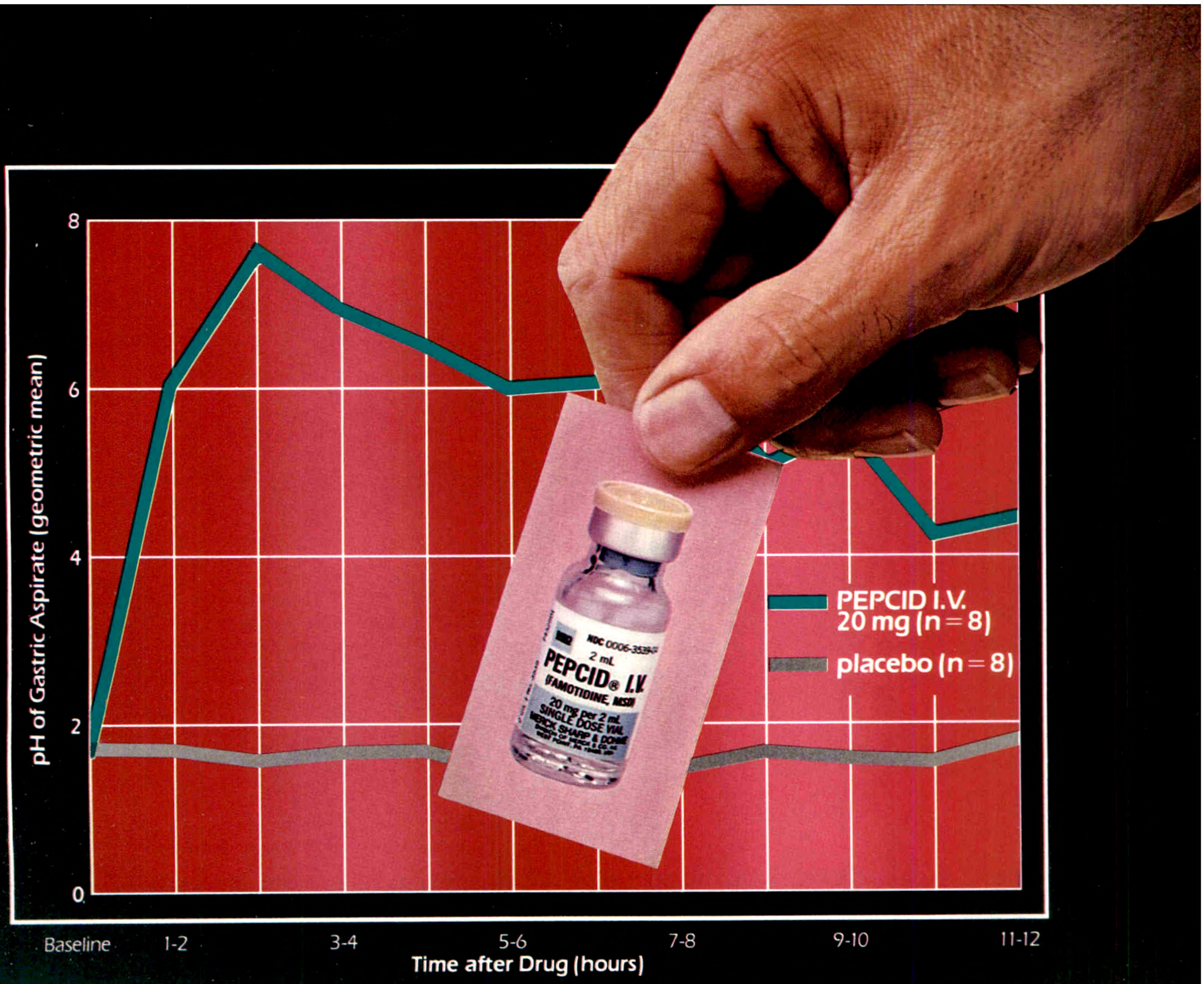

A double-blind, placebo-controlled study[1] involving eight volunteer hypersecretor subjects. The pH of gastric aspirates was measured hourly for 12 hours following single intravenous doses. PEPCID I.V. maintained the mean gastric pH above 4.0 at all time points throughout the 12-hour period with one 20-mg I.V. dose.

1. Ryan, J.R. et al.: Comparison of effects of oral and intravenous famotidine on inhibition of nocturnal gastric acid secretion, Am. J. Med. 81 (Suppl. 4B): 60-64, October 24, 1986.

INJECTION, 20 mg/2 mL

q12h **Pepcid® IV**

(Famotidine|MSD)

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INJECTION
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(Famotidine|MSD)
20 mg per 2 mL

Contraindications: Hypersensitivity to any component.

Precautions: ***General:*** Symptomatic response to therapy does not preclude the presence of gastric malignancy.

Patients with Severe Renal Insufficiency: Longer intervals between doses or lower doses may be needed in patients with severe renal insufficiency (creatinine clearance <10 mL/min) to adjust for the longer elimination half-life of famotidine (see Clinical Pharmacology and Dosage and Administration sections of Prescribing Information).

Information for Patients: The oral suspension should be shaken vigorously for 5 to 10 seconds prior to each use, and unused constituted oral suspension should be discarded after 30 days.

Drug Interactions: No drug interactions have been identified. Compounds tested in man include warfarin, theophylline, phenytoin, diazepam, aminopyrine, and antipyrine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In rats and mice given oral doses up to approximately 2,500 times the recommended human dose for active duodenal ulcer, there was no evidence of carcinogenic potential; at these doses in rats, fertility and reproductive performance were not affected. No evidence of a mutagenic effect was observed.

Pregnancy: *Pregnancy Category B*—There are no adequate or well-controlled studies in pregnant women. Use during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether famotidine is secreted into human milk; however, it is secreted into the milk of lactating rats. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: No dosage adjustment is required based on age but may be necessary in severe renal impairment (see Clinical Pharmacology section of Prescribing Information).

Adverse Reactions: The adverse reactions listed below have been reported during domestic and international clinical trials in approximately 2,500 patients. In the placebo-controlled clinical trials, the incidence of adverse experiences with PEPCID Tablets 40 mg at bedtime was similar to that with placebo.

Incidence Greater than 1%: The following adverse reactions have been reported to occur in more than 1% of patients on therapy with PEPCID in controlled clinical trials and may be causally related to the drug: headache (4.7%), dizziness (1.3%), constipation (1.2%), and diarrhea (1.7%).

Causal Relationship Unknown: The following other adverse reactions have been reported infrequently and within each category are listed in order of decreasing severity. The relationship to therapy with PEPCID has been unclear in many cases. *Body as a Whole*—Fever, asthenia, fatigue. *Cardiovascular*—Palpitation. *Gastrointestinal*—Cholestatic jaundice, liver enzyme abnormalities, vomiting, nausea, abdominal discomfort, anorexia, dry mouth. *Hematologic*—Thrombocytopenia. *Hypersensitivity*—Anaphylaxis, angioedema, orbital or facial edema, urticaria, rash, conjunctival injection. *Musculoskeletal*—Musculoskeletal pain, arthralgia. *Nervous System/Psychiatric*—Grand mal seizure; psychic disturbances including depression, anxiety, decreased libido, hallucinations; paresthesia; insomnia; somnolence. *Respiratory*—Bronchospasm. *Skin*—Alopecia, acne, pruritus, dry skin, flushing. *Special Senses*—Tinnitus, taste disorder.

The adverse reactions reported for PEPCID Tablets may also occur with PEPCID Oral Suspension or PEPCID I.V.; in addition, transient irritation at the injection site has been observed with PEPCID I.V.

AV block has been reported with other H_2-receptor antagonists, but not with famotidine.

Management of Overdosage: There is no experience to date with deliberate overdosage. Up to 640 mg/day have been given to patients with pathological hypersecretory conditions with no serious adverse effects. In the event of overdosage, treatment should be symptomatic and supportive. Unabsorbed material should be removed from the gastrointestinal tract, the patient should be monitored, and supportive therapy should be employed.

Dosage and Administration: ***Duodenal Ulcer:*** The recommended adult oral dosage for active duodenal ulcer is 40 mg h.s.; most patients heal within 4 weeks, and it is rarely necessary to use the full dosage for longer than 6 to 8 weeks. A regimen of 20 mg b.i.d. is also effective. For maintenance therapy, the recommended oral dosage is 20 mg h.s.

Benign Gastric Ulcer: The recommended adult oral dosage for active benign gastric ulcer is 40 mg h.s.

Pathological Hypersecretory Conditions (e.g., Zollinger-Ellison Syndrome, Multiple Endocrine Adenomas): The dosage varies with the individual patient; the recommended adult oral starting dosage is 20 mg q6h, but some patients may require a higher starting dosage. Dosages should be adjusted to individual patient needs and continued as long as clinically indicated; up to 160 mg q6h have been administered to some patients with severe Zollinger-Ellison syndrome.

Oral Suspension: The oral suspension may be substituted for tablets.

Directions for Preparing PEPCID Oral Suspension: Prepare suspension at time of dispensing. Slowly add 46 mL Purified Water. Shake vigorously for 5 to 10 seconds immediately after adding the water and immediately before use.

Stability of PEPCID Oral Suspension: Unused constituted oral suspension should be discarded after 30 days.

Intravenous Administration: In some hospitalized patients with pathological hypersecretory conditions or intractable ulcers or in patients who are unable to take oral medication, the recommended intravenous dosage is 20 mg q12h. For preparation of intravenous solutions for injection or infusion and for compatible diluents, please see Prescribing Information. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Concomitant Use of Antacids: Antacids may be given concomitantly if needed.

Dosage Adjustment for Patients with Severe Renal Insufficiency: In patients with severe renal insufficiency (creatinine clearance less than 10 mL/min), the elimination half-life of famotidine may exceed 20 hours, reaching approximately 24 hours in anuric patients. Although no relationship of adverse effects to high plasma levels has been established, to avoid excess accumulation of the drug, the dosage may be reduced to 20 mg h.s. or the dosing interval may be prolonged to 36 to 48 hours as indicated by the patient's clinical response.

How Supplied: Tablets, containing 20 mg or 40 mg famotidine, with hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxides, magnesium stearate, microcrystalline cellulose, starch, talc, and titanium dioxide as inactive ingredients, in unit-of-use bottles of 30 and unit-dose packages of 100; Oral Suspension, containing 40 mg famotidine per 5 mL after constitution with 46 mL Purified Water, with citric acid, flavors, microcrystalline cellulose and carboxymethylcellulose sodium, sucrose, and xanthan gum as inactive ingredients, and sodium benzoate 0.1%, sodium methylparaben 0.1%, and sodium propylparaben 0.02% added as preservatives, in bottles of 400 mg famotidine for constitution; Solution for intravenous injection, containing 10 mg famotidine per mL, with L-aspartic acid 4 mg, mannitol 20 mg, and Water for Injection q.s. 1 mL as inactive ingredients, and benzyl alcohol 0.9% added as preservative to the multidose vial, as 10x2-mL single-dose vials and as 4-mL vials.

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Twenty-Three-Year Follow-up of Separated Ischiopagus Tetrapus Conjoined Twins

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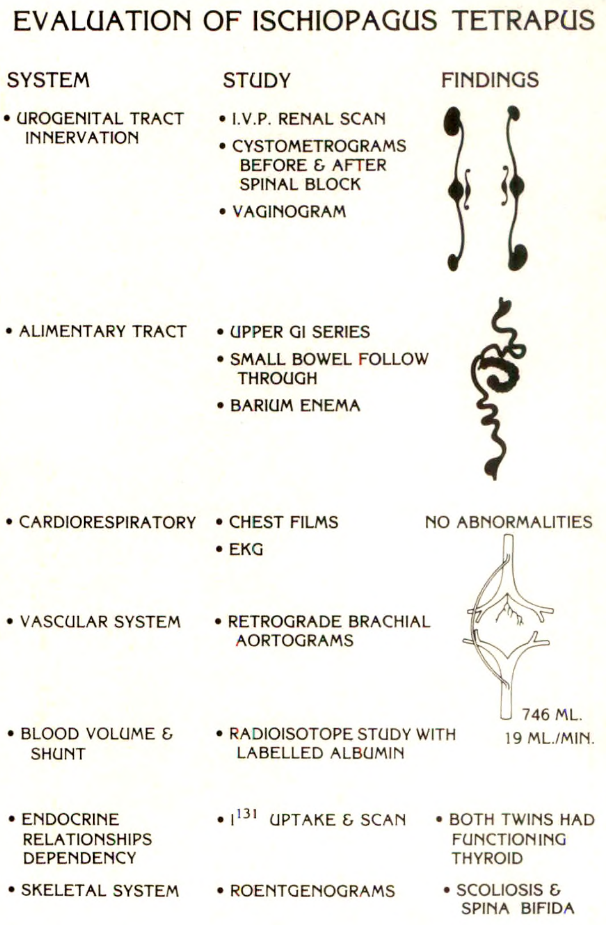
This paper presents a 23-year follow-up of the separation of ischiopagus tetrapus conjoined twins reported in *Annals of Surgery* in December 1966. One twin died of septicemia at age 2 years after bilateral pelvic osteotomies for the treatment of her marked pelvic diastasis. The surviving twin has done reasonably well, and her most significant problem is related to her musculoskeletal system. She has an increasing T7-10, L-1 apex right congenital scoliosis with wedged vertebra at T-10, as well as marked pubic diastasis and bilateral subluxation of her hips. This has resulted in a somewhat aberrant physical appearance and a "waddling" gait. Her colostomy functions well and she has normal renal and bladder function. This patient's history illustrates that many problems remain after successful separation of conjoined twins. However these problems are manageable and do not preclude the possibility that such a patient may be a productive member of society.

There are more than 600 publications in the literature concerning conjoined twins and they treat many topics, including prenatal diagnosis, obstetrical management, labor and delivery, neonatal care, preoperative evaluation, anesthetic management, and various aspects of surgical separation.[1-15] However there have been few reports on the long-term follow-up of conjoined twins after surgical separation. This paper reports on the follow-up of ischiopagus tetrapus twins separated at our institution and reported in *Annals of Surgery* in 1966, with a review of the literature on the separation of all ischiopagus conjoined twins.

The incidence of conjoined twins is approximately 1 in 25,000 to 1 in 80,000 births, with most authors quoting an average incidence of 1 in 50,000 births.[6,14,16] However



EVALUATION OF ISCHIOPAGUS TETRAPUS

SYSTEM	STUDY	FINDINGS
• UROGENITAL TRACT INNERVATION	• I.V.P. RENAL SCAN • CYSTOMETROGRAMS BEFORE & AFTER SPINAL BLOCK • VAGINOGRAM	
• ALIMENTARY TRACT	• UPPER GI SERIES • SMALL BOWEL FOLLOW THROUGH • BARIUM ENEMA	
• CARDIORESPIRATORY	• CHEST FILMS • EKG	NO ABNORMALITIES
• VASCULAR SYSTEM	• RETROGRADE BRACHIAL AORTOGRAMS	
• BLOOD VOLUME & SHUNT	• RADIOISOTOPE STUDY WITH LABELLED ALBUMIN	746 ML. 19 ML./MIN.
• ENDOCRINE RELATIONSHIPS DEPENDENCY	• I^{131} UPTAKE & SCAN	• BOTH TWINS HAD FUNCTIONING THYROID
• SKELETAL SYSTEM	• ROENTGENOGRAMS	• SCOLIOSIS & SPINA BIFIDA

FIG. 1. Preoperative evaluation of potentially joined or dependent organ systems.

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TABLE 1. *Surgical Separation of Conjoined Twins*

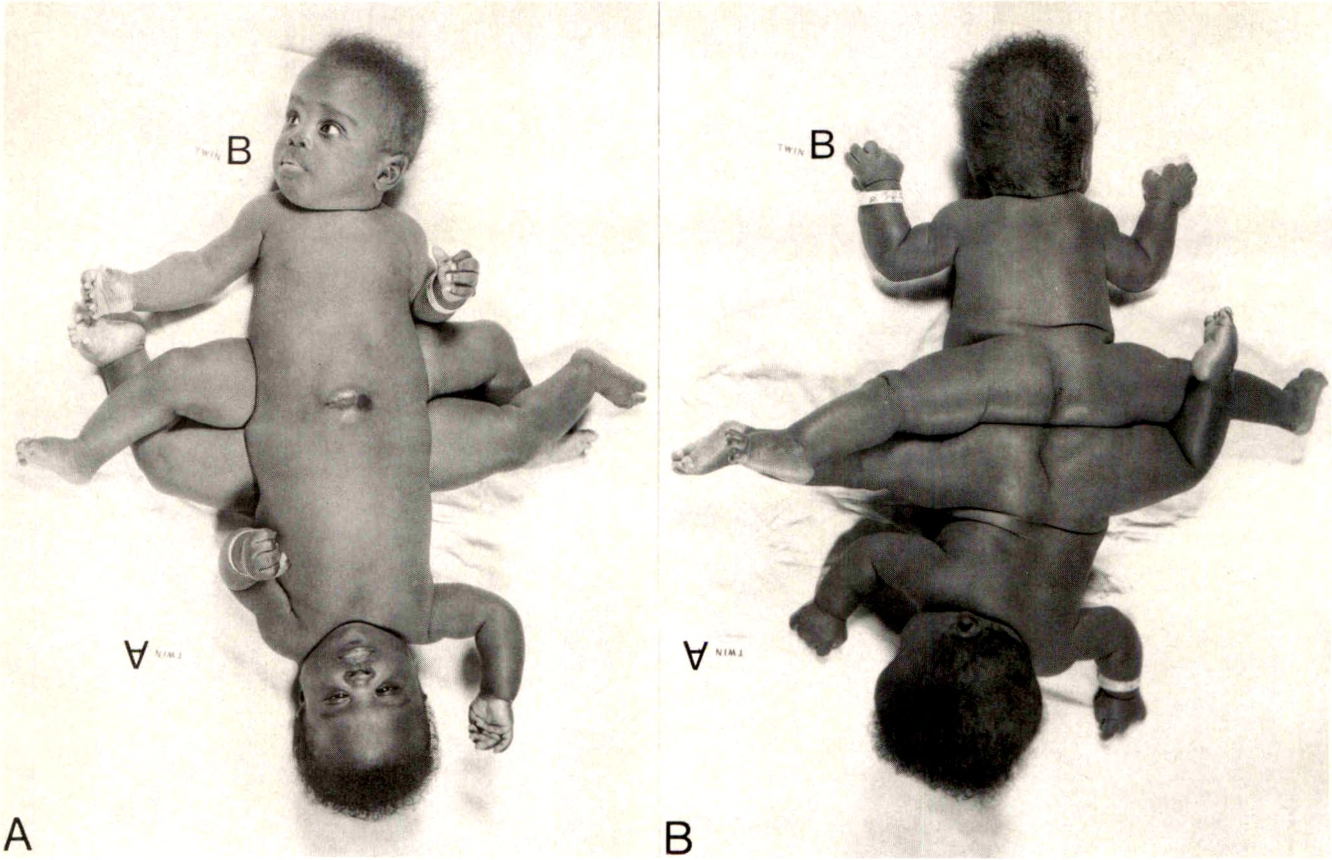
Year	Author and Reference	Sex	Type	Age at Separation	Shared Organs	Indication of Separation	Results (Follow-up)	
							Twin 1	Twin 2
1955	Spencer[18,22]	F	Isch Tet	18 hrs.	Liver bridge, terminal ileum, colon, anus, pelvic organs	Emergent; demise of twin one	D (sacrificed)	S (age 10 mos.)
1966	Eades[19]	F	Isch Tet	7 mos.	Colon, anus, pelvic organs	Elective	S (age 23 yrs.)	S (died at 2 years)
1967	Akiyama[24]	F	Isch NS	3 mos.	NS	NS	S	D
1968	Mestle[21,23]	F	Isch Tri	16.5 mos.	Colon, anus	Elective	S (age 20 yrs.)	S (age 20 yrs.)
1969	Poradowsky[26]	F	Isch Tet	NS	Pelvic organs, cloaca	Emergent: intestinal obstruction	D	D
1969	Borden[27]	F	Isch Tet	NS	Ileum, colon, liver bridge	Elective	S	S
1969	Koop[28]	NS	Isch Tet	NS	NS	NS	S	S
1971	Rossi[29]	F	Isch Tet	NS	Terminal ileum, colon	Elective	S (age 2 yrs.)	S (age 2 yrs.)
1971	Borde[30]	F	Isch Tri	3 yrs.	Colon, rectum, liver bridge, bladders	Elective	D (10 hrs. postop.)	D (36 hrs. postop.)
1971	Mayell[31]	NS	Isch Tri	NS	NS	NS	D	S
1971	Bankole[32,33]	F	Isch Tet	60 hrs.	Ileum, colon, bladder, cloaca	Emergent: intestinal and urethral obstruction	D (30 hrs. postop.; congestive heart failure)	D (congestive heart failure)
1971	Furman[34]	F	Isch Tet	4 days	Liver bridge, colon, anus, pelvic organs	Emergent: intestinal obstruction	S	S
1974	Cywes[35]	F	Isch Tet	7 days	Bladder, cloaca	Emergent: intestinal obstruction	D (6 days postop. sepsis)	D (sacrificed anencephaly)
1974	Koop[28]	NS	Isch Tet	NS	NS	NS	S	S
1976	Akiyama[24]	F	Isch Tet	3 mos.	Terminal ileum, colon, rectum, bladder, cloaca	Elective	S	S
1978	Rosenburg[20,21]	F	Isch Tet	13 mos.	Colon, anus, pelvic organs	Elective	S (age 13 yrs.)	D (1 yr. postop. aspiration)
1979	Hung[36]	M	Isch Tri	2.75 yrs.	Liver bridge, terminal ileum, colon, penis	Elective	S (age 9 yrs.)	S (age 9 yrs.)
1979	Chao[1]	M	Isch Tet	2.75 yrs.	Liver bridge, colon, anus, penis	Elective	S	S
1981	Rector[37]	F	Isch Br	11 mos.	Colon, rectum, bladder, liver bridge	Elective	S (age 8 yrs.)	S (age 8 yrs.)

1981	Somasundaram[38]	F	Isch Tet	7 mos.	Colon	Elective	S (age 4.5 yrs.)	S (age 4.5 yrs.)
1981	Vottler[8]	M	Isch Tri	NS	NS	NS	S	S
1981	Vottler[8]	F	Isch Tri	NS	NS	NS	S	D
1981	Vottler[8]	F	Isch Tri	NS	NS	NS	S	S
1982	Somasundaram[38]	F	Isch Tet	4 mos.	Colon, urethra	Elective	S (age 3.25 yrs.)	S (age 3.25 yrs.)
1982	Grantzow[39]	M	Isch Tri	2.5 yrs.	Terminal ileum, colon, pelvic organs, liver	Elective	S (died at age 3 yrs. 8 mos.; sepsis	S (age 3 yrs. 8 mos.)
1983	Grantzow[40]	M	Isch Tet	10 mos.	Terminal ileum, colon, pelvic organs	Elective	S	S
1984	Harrison[9]	M	Isch Tet	4 days	Colon, Penis, bladder	Emergent; intestinal obstruction	S (6 wks. postop.; female assignment)	S (6 wks. postop.; male)
1984	Savickis[41]	M	Isch Tri	2.5 yrs.	Liver bridge, colon, bladder, penis	Elective	S	S
1984	James[2]	M	Isch Tri	29 mos.	Colon, liver, penis, prostate	Elective	S (age 2 yrs.)	S (age 2 yrs.)
1984	Ross[3], O'Neill[42]	F	Isch Tri	4 mos.	Liver bridge, colon, terminal ileum	Elective	S (age 2 yrs.)	S (age 2 yrs.)
1984	Olcay[16]	M	Isch Tet	? days	Pelvic organs	Emergent: demise of twin one	D (14 hrs. postop.)	D (intraoperatively)
1985	Zuker[43]	M	Isch Tet	9 mos.	Colon, penis	Elective	S (3 mos. postop.)	S (3 mos. postop.)
1986	Chatterjee[44]	F	Isch Tet	1 yr.	Colon, anus, pelvic organs	Elective	S (6 mos. postop.)	S (6 mos. postop.)

Isch, ischiopagus; Tet, tetrapus; Tri, tripus; Bi, bipus; F, female; M, male; NS, not stated; S, survived; D, died.

Pelvic organs are as described in the text.

Listed year is year of separation or year of publication.



FIGS. 2A and B. (A) Front and (B) posterior view of ischiopagus tetrapus twins at 7 months of age.

60% are stillborn, yielding an incidence of conjoined twins alive at birth of 1 in 200,000. In Africa the incidence has been quoted as high as 1 in 14,000 deliveries, thus suggesting an increased frequency in blacks.

Conjoined twins are classified by their most prominent site of connection with the Greek root *pagus* (that which is fixed). Such sites may include the thorax (thoracopagus), abdomen (omphalopagus), pelvis (pyopagus), or skull (craniopagus). Thoracopagus is the most common classification, accounting for 40% of reported cases; omphalopagus number 33%; pyopagus, 19%; ischiopagus, 6%; and craniopagus, 2%.[8,17] Ischiopagus twins are joined at the pelvis and they usually have three (tripus) or four limbs (tetrapus). The intestinal tracts usually join at the terminal ileum, which empties into a single colon. Four kidneys and two bladders are usually present. One ureter from each twin frequently crosses the midline and empties into the bladder of the other. Male twins may have fusion of the genitourinary tract distal to the bladder but they usually have four gonads. Female twins usually have four ovaries, two uteri, and two sets of external genitalia on either side of a single anus. Vaginal anomalies and rectovaginal communication are not uncommon.

To date there have been 33 attempts at surgical separation of ischiopagus conjoined twins (Table 1). The first separation of ischiopagus twins with survival of one twin was performed by Spencer[18] in 1955. In 1966 Eades and Thomas[19] reported the first separation of ischiopagus twins with survival of both twins.

We report a 23-year follow-up of the surviving twin.

Case Report

The twins were born April 6, 1965 and transferred to the North Carolina Memorial Hospital. Studies revealed the following (Fig. 1):(A) A widely open, semicircular pelvis with fusion of each pubic symphysis with the corresponding symphysis of the opposing twin. (B) Thoracolumbar scoliosis and spina bifida involving the lower lumbar vertebrae in both twins. (C) A common distal ileum, cecum, and colon terminating in a rectal fistula. (D) Two laterally placed bladders receiving ureters from both twins with bilateral innervation of both bladders. (E) Bilateral arterial supply to the pelvic organs and a direct continuation of the superior mesenteric artery of infant A to infant B. Bilateral blood supply to the common colon from the inferior mesenteric artery of each twin. (F) Absence of kidney and ureter on the left side of infant A.

The twins were separated at age 7 months on November 8, 1965 (Fig. 2). The union between the bony pelvis of the infants was separated. Each infant was provided with one kidney, ureter, and bladder, essentially complete internal genitalia, a portion of colon, and a small intestine of normal length. Both twins were given a permanent colostomy in the right midabdomen. At the time of publication (4 months after operation), the twins were doing well and undergoing progressive splinting to restore a more normal position at the hips and permit future ambulation because both twins had a marked pubic diastasis and bilateral coxa vara.

Twin A's postoperative course was complicated by the development of phlegmasia cerulea dolens secondary to thrombophlebitis caused by a venous catheter high in her right axillary vein. She subsequently developed ischemic necrosis of skin on her distal right forearm requiring multiple debridements and skin grafts. This progressed to chronic osteomyelitis of her right distal ulna and radius. At approximately 3 years of age and two days after undergoing bilateral pelvic osteotomies for treatment of marked pubic diastasis, she died of cardiac arrest. Autopsy revealed streptococcal septicemia, principally in her lungs and brain.

Twin B's most significant problem is related to her musculoskeletal system; she has an increasing T7-10, L-1 apex right congenital scoliosis with wedged vertebrae at T-10, as well as marked pubic diastasis and bilateral subluxation of her hips. Recommendation for surgical amelioration of these problems was not accepted by the patients family. At age 4 years her scoliosis measured 75 degrees; at age 6 years it measured 108 degrees; and at age 20 years it was 107 degrees (Fig. 3). She continues to have a widely separated pubic symphysis (Fig. 4). She also has a marked kyphosis of 83 degrees.

Menarche occurred at approximately age 12 to 13. In 1981 at age 16, she underwent a right salpingo-oophorectomy for removal of a symptomatic (painful) right ovarian cyst measuring 8 cm in diameter. Pathologic findings were those of endometriosis with an endometrial cyst. She has severe lower abdominal pain in association with menses such that she must remain in bed for two to four days. This started in 1985 and is still a recurring problem. The overall findings are consistent with endometriosis and she has been treated with oral contraceptive therapy.

She has always been a bright student and maintained a B average in the 8th grade; however she dropped out of school in the 11th grade. She indicates that this was because of a fall that resulted in discomfort in her left hip such that she could not walk more than one block without stopping.

Her mother died in 1984 of pneumonia and because she is the oldest in the household she assumed the responsibility of the household for herself and her two brothers, aged 16 and 10 years. Her grandmother and aunt live nearby.

Twin B is now 23 years old and was last seen in 1985 with full body photos (Fig. 5).

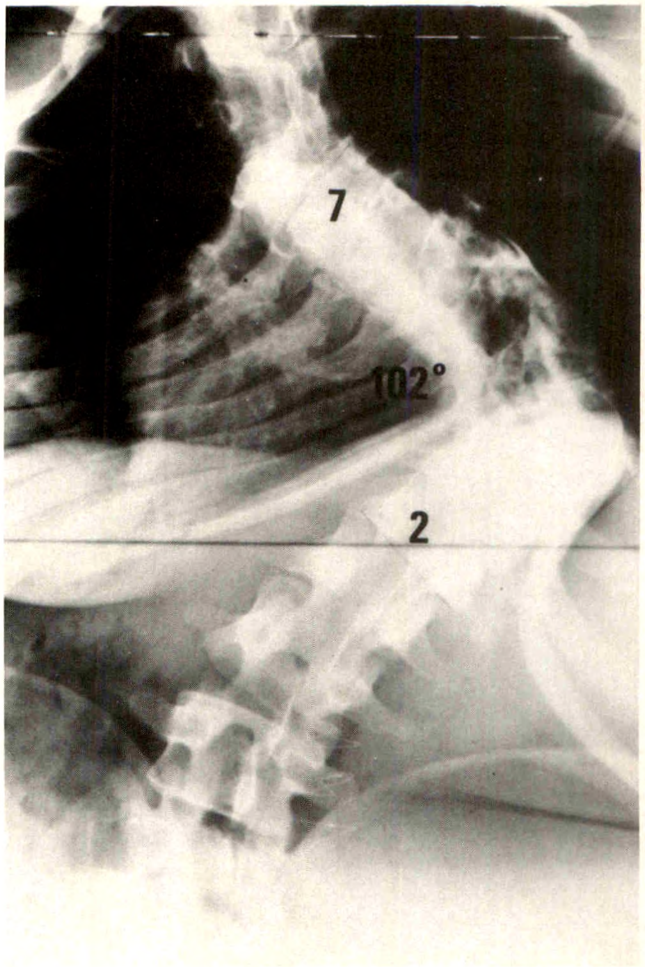


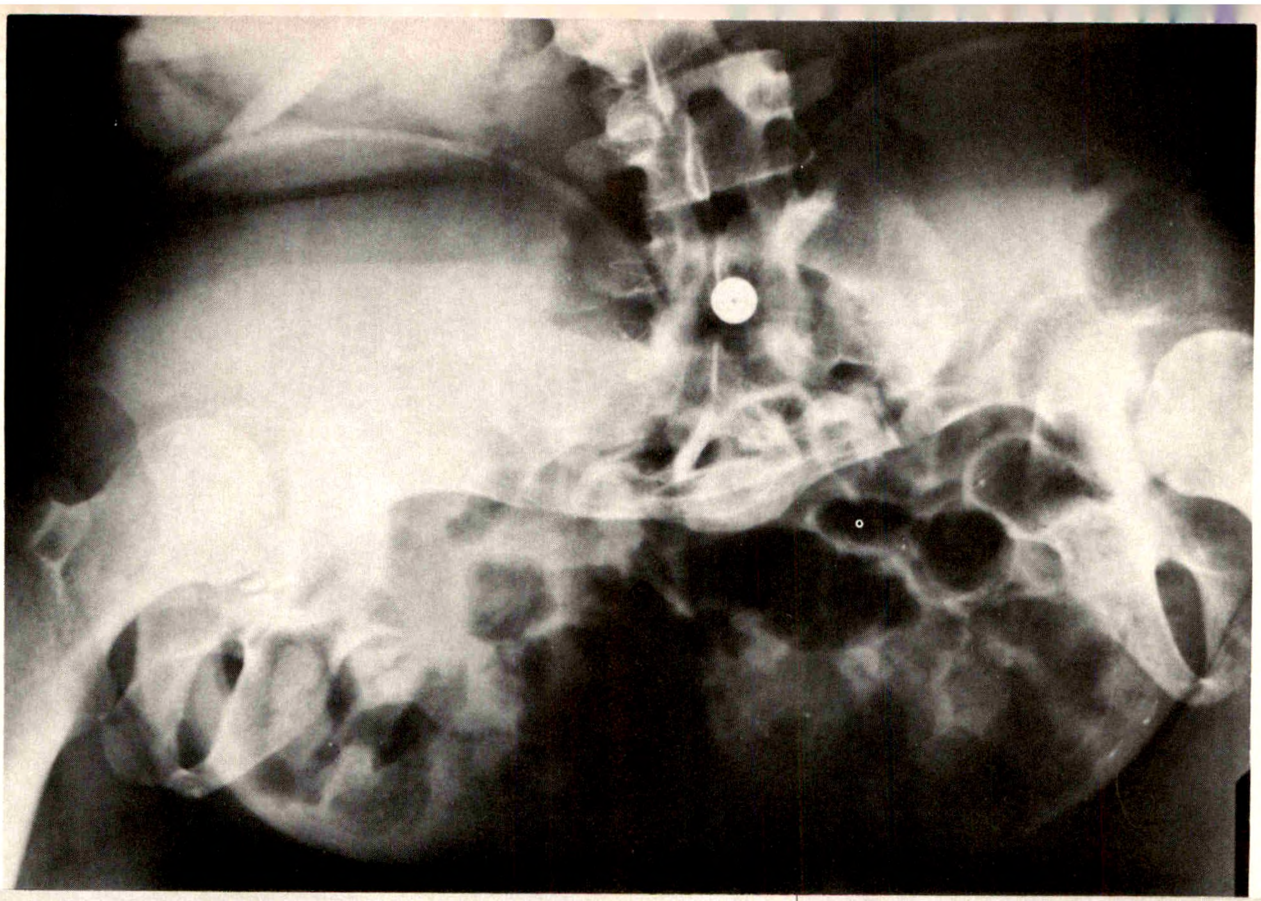
FIG. 3. Radiograph demonstrating scoliosis of 107 degrees at age 21 years.

Discussion

Of 33 attempts at surgical separation of ischiopagus conjoined twins, 11 were ischiopagus tripus and 20 were ischiopagus tetrapus (Table 1). One case was not declared as tripus or tetrapus and another was ischiopagus bipus (sharing only two legs). Sixty-seven per cent of these twins were female (tetrapus, 70%; tripus, 45%). Shared organs included a common terminal ileum in 27.3% (9 cases) and a colon in 69.7% (23 cases). The perioperative mortality rate for ischiopagus conjoined twins was 18.8%, with 52 of 66 twins living (excluding two twins who had to be sacrificed to save their conjoined siblings). There was no difference in perioperative mortality rate between ischiopagus tetrapus and tripus twins. Before 1975 the perioperative mortality rate was 38.46% (16 of 26 twins living) and from 1975 through 1987 it was reduced to 10% (36 of 40 twins living). Analysis of the effect of emergent operation on outcome revealed an overall perioperative mortality rate of 18.8% compared to 64.3% with emergent operation and 5.26% with elective operation.

Reports of the follow-up of surgically separated twins are few. Rosenburg[20] reported the successful separation of ischiopagus tetrapus twins in 1978 with the survival of both twins. One twin died 1 year after operation from aspiration of a bean, the other has been partially deaf since birth, has had problems with urinary tract infections and hematuria, has a somewhat disturbed gait as a result of pubic diastasis, but otherwise is a healthy, sixteen year old.[21]

Spencer[18] reported the successful separation of ischiopagus tetrapus twins in 1955. One twin was deformed and moribund. The other twin was lost to follow-up at 10 years of age but at that time was doing quite well except for her short stature and abnormal gait due to the absence of symphysis pubis.[22] Mestal[23] reports ischiopagus tripus



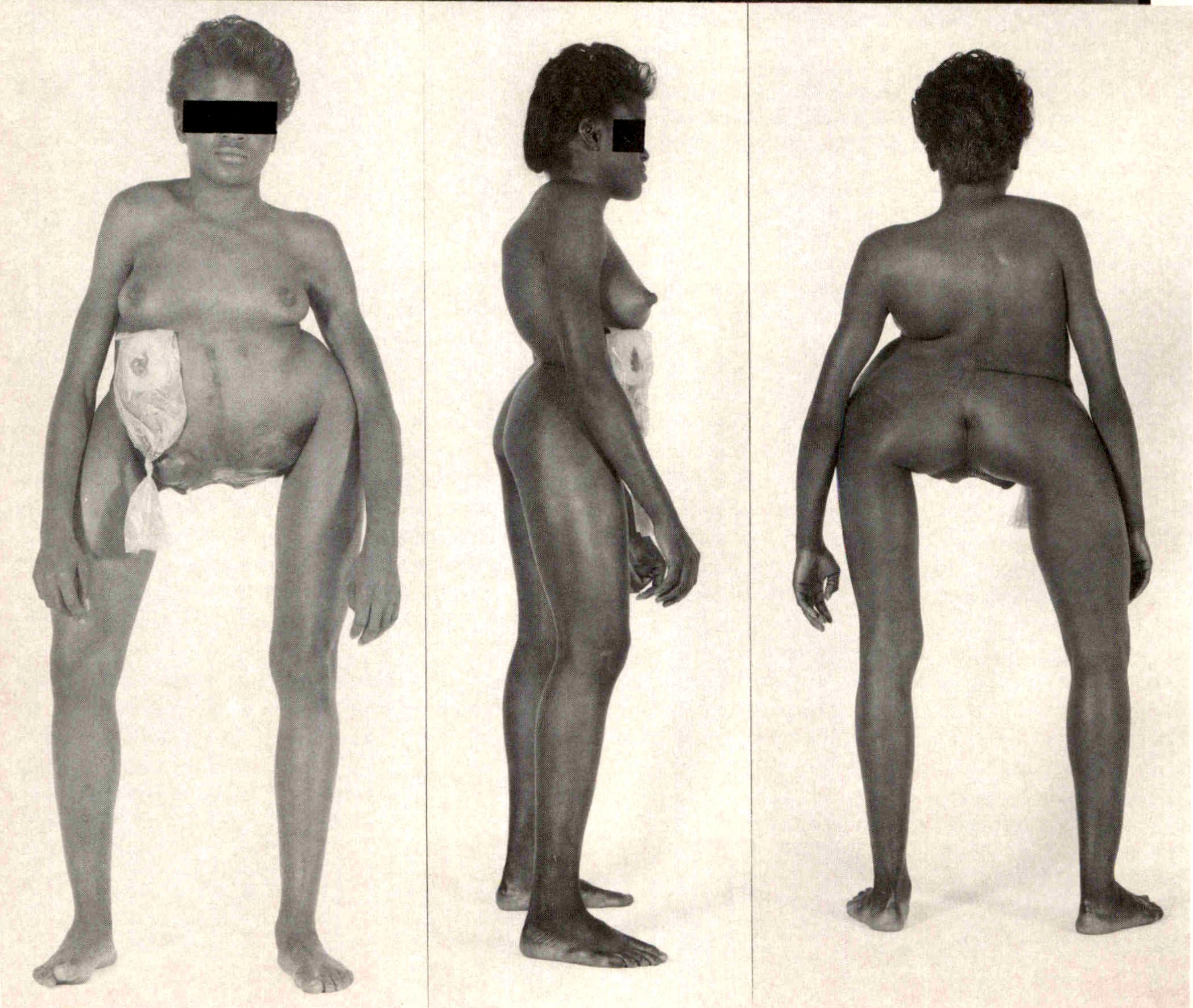


FIG. 4. Radiograph demonstrating widely separated pubic symphysis at age 20 years.

FIGS. 5A–C. (A) Front, (B) lateral, and (C) posterior appearance at age 20 years.

twins who are functioning with a prosthesis and doing quite well 20 years after surgical separation.

Successfully separated ischiopagus twins require long-term rehabilitation and follow-up, particularly with regards to orthopaedic, urologic, and gynecologic problems. However, despite all these problems, separation can enable these patients to become happy, intelligent, and potentially productive members of society.

Acknowledgments

The authors thank Ms. Karen Jordan and Ms. Doris Eason for expert manuscript preparation.

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Book Reviews

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Jonathan E. Rhoads: Eightieth Birthday Symposium. Clyde F. Barker and John M. Daly. 517 pp. Philadelphia: J. B. Lippincott, 1989. $80.00.

THIS IS AN EXTRAORDINARY collection of contributions prepared for the Eightieth Birthday Symposium of the master teacher, investigator, clinician, and surgical statesman, Jonathan E. Rhoads. These essays are written by his former pupils in the Surgical Residency Training Program at the University of Pennsylvania. It is astonishing to reflect on the number and quality of these surgical scholars whom he has trained because each is an acknowledged leader in contemporary academic surgery. The organizing committee selected 17 individuals to make scientific presentations. Each is singularly outstanding, and these treatises represent a unique resource on each subject. The first chapter is by Clyde F. Barker, the John Rhea Barton Professor and Chairman of the Department of Surgery at the University of Pennsylvania. It is an elegant review of the current status of the Department at Pennsylvania, which for more than 200 years has served as a prime source of the nation's greatest surgeons. This unique department was led by Isidore Ravdin in the 1940s and 1950s and was brought to its present pinnacle of academic significance by Jonathan Rhoads. A host of his trainees have become professors and chairmen of departments of surgery throughout the nation. It is appropriate that one of the most recently endowed Chairs is the Jonathan E. Rhoads Professorship of Surgery. Clyde Barker provides excellent summaries of the current investigations being pursued in this notable Department that has been long recognized as a classic role model.

Others among the 17 surgeons selected for presentations were Edward M. Copeland III, who discussed work on intravenous hyperalimentation in cancer; P. William Curreri, who spoke on microvascular filtration in burned and nonburned tissues; Gordon K. Danielson, who presented experiences with the surgical management of pulmonary atresia combined with ventricular septal defect and hypoplastic confluent pulmonary arteries; Stanley J. Dudrick, who discoursed on regression of atherosclerosis by the intravenous infusion of specific biochemical nutrient substrates; and Cleon W. Goodwin, who presented data showing that colloid increases lung water after massive fluid resuscitation. Continuing were others equally noted in their fields, including James D. Hardy on the first heart and lung transplants in man, John M. Howard on acute pancreatitis, R. Scott Jones reviewing prognostic factors in carcinoma of the colon and rectum, Edwin L. Kaplan presenting nuclear DNA analysis of insulinomas and gastrinomas, and F. Carter Nance on abdominal trauma. The parade of stars proceeded with a discussion of emergency portacaval shunts by Marshall J. Orloff, the role of intraoperative ultrasound of the liver by Francis E. Rosato, and a review of oxygen delivery by Harvey J. Sugerman. The concluding presentations of the Symposium were also classic works with a discussion by James C. Thompson on gastrointestinal hormones, a review of coarctation of the aorta in infancy by John A. Waldhausen, and studies on positive nitrogen balance with human growth hormone and hypocaloric intravenous feedings by Douglas W. Wilmore.

In the second half of this remarkable text are 37 commemorative articles also written by former students of Jonathan Rhoads. These cover a wide range of surgical issues that vary from "Reminiscences of the Surgical Services of the Hospital of the University of Pennsylvania from 1931 to 1935" by Charles W. McLaughlin to "The Current Crisis in AIDS" by Surgeon General C. Everett Koop. Delightful sketches of the life and contributions of Jonathan Rhoads that were given at the Eightieth Birthday Dinner by Clyde F. Barker, Whitfield J. Bell, Jr., William P. Longmire, Jr., Francis D. Moore, and Harris B. Shumacker, Jr., are also included. These provide, in a very engaging manner, eloquent expressions of recognition of the many contributions made by the surgical giant honored that day. William P. Longmire, Jr., summarized Jonathan Rhoads' career, concluding that "through many other crucial tests of character that I have witnessed over the past thirty years, Jonathan continues to stand tall as a friend and, as a colleague with his unique intelligence, his unfailing loyalty, his ready wit and humor, and with a kind, sound judgment that wins the respect of us all."

In presenting a biography of Walter B. Cannon, the noted professor of physiology at Harvard, to Dr. Rhoads, Francis D. Moore said, "it symbolizes the many friendly gestures between Boston and Philadelphia, despite all those ancient rivalries dealt with in Mr. Balzel's book, and is most fitting for me to present from the Harvard faculty." Quite appropriately Clyde Barker concluded, "since he has achieved virtually everything in life, it is difficult to wish something for him that he hasn't already had." With such superlative tributes as these, this commemorative volume will long serve as a scholarly reference in scientific surgery. The editors are to be warmly praised for publishing this unique collection in a single volume available to all. It can be recommended to the profession everywhere as an essential and updated source of the major topics in contemporary surgery. It is a master work and surely its contents will be frequently cited in the literature of the future.

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The Handbook of Surgical Intensive Care: Practices of the Surgery Residents at The Duke University Medical Center, 2nd Ed. H. Kim Lyerly. 665 pp. Chicago: Year Book Medical Publishers, 1989. $18.95.

THIS IS THE SECOND edition of a notable compendium that provides a concise, yet comprehensive, review of the clinical problems evident in the Surgical Intensive Care Unit (SICU). This edition, as was the first, is written by surgery residents of Duke University for residents. Dr. Lyerly has drawn on the considerable experience of these residents and extensive literary reviews to strengthen the personal observations and experiences that confront the surgical resident and critical-care physician in the SICU. Surgical considerations with special emphasis on patient management after major operative procedures are stressed in each section.

The editor has organized this volume anatomically by organ system with emphasis on specialty problems confronting residents in the SICU including nutrition, delirium, microvascular circulation, endocrinology, traumatology, temperature regulation, infection, burn treatment, cardiac monitoring, and medications. An extensive bibliography is provided at the end of each chapter or section to supplement the text. The index is complete and informative and allows the reader to search rapidly for organ systems or metabolic derangement at a glance. There are supplementary tables and diagrams that provide a rapid summation and review of pertinent data. The section on medications is a most useful summation of pertinent, contemporary drugs listed in their generic forms along with trade names, thus facilitating for the reviewer a rapid perusal of their use, form, and dosage in the clinical setting. In the SICU a reference of such pharmacologic applications is especially valuable to the junior house officer when faced with emergent decisions concerning life-threatening illnesses. These sections are complimented by an appendix that allows a succinct review of formulas (physiologic, mathematic, metabolic, and so on) that are frequently used in patient management but rarely committed to memory due to their complexity.

This second volume will be a useful and welcomed addition to the armamentarium of residents and staff as they care for the critically ill patient. The strength of the book is its exceptional and complete organization with comprehensive review of various organ systems. It is highly readable, useful, and accessible, with appropriate applications of tables and charts to reinforce the basic concepts in critical care medicine. Considering the effort of the editor to be comprehensive yet concise, with production of a tome that details sound physiologic principles applicable to patient management for the emergency condition, Dr. Lyerly has clearly achieved his goal. Because the volume is extensive, the book is bulky and may be difficult to carry in one's pocket.

This 2nd edition of **The Handbook of Surgical Intensive Care** is highly recommended to residents and interns of all surgical disciplines. It is masterfully organized into a readable reference volume that should be considered an essential part of the library of all residents in the surgical and critical care discipline. This edition should prove equally valuable to the nursing staff and faculty of SICUs involved in the care of the critically ill. The editor has provided a rapid-review reference volume that will be invaluable on a daily basis as an aid to physicians in administering high-quality clinical care in the intensive care setting.

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Management of Esophageal Disease. David B. Skinner and Ronald H. R. Belsey. 895 pp. Philadelphia: W.B. Saunders, 1988. $145.00.

THIS BOOK IS written by two surgeons who have dedicated their professional lives to solving complex esophageal problems. They make an important professional contribution by compiling a complete textbook in 12 sections that cover most aspects of esophageal disease.

Esophageal development, macroscopic and microscopic anatomy, and physiology are discussed succinctly. The chapter on investigation of esophageal disease emphasizes appropriately that symptoms cannot be used as an accurate basis to establish a diagnosis and determine the indication or the success of treatment in reflux disease. The chapter on radiology is excellent and emphasizes how radiologic studies complement other facets of investigation. A review of indications and techniques for rigid and flexible endoscopy is provided. Investigation techniques that should be available in the esophageal laboratory are discussed concisely and clearly.

There is an excellent chapter by Charles Winans on the medical management of reflux disease. A safe approach to the strictured or obstructed esophagus follows. Because the esophagus is a frequent target of psychosomatic disorders, it is appropriate to find a chapter on this topic. However a review of the effects of the various psychological disorders on esophageal function would have been a welcome addition to this chapter.

There is an impressive section on the principles that should guide surgical treatment of esophageal disorders. The short history on esophageal surgery is enlightening and humbling and is followed by a philosophic guide to the management of esophageal disease. These two chapters, written with the patina of experience, present a clear orientation toward objectivity, good judgment, and delicate technical management. The chapters on surgical exposure of the esophagus, anastomotic technique, and reconstruction with the colon are finely detailed and especially well illustrated. The views on the use of the stomach for reconstruction in benign disease should be looked at with the perspective of the recent literature.

Five chapters on congenital abnormalities of the esophagus emphasize that the same principles of management should govern pediatric esophageal surgery and that it should not be sequestrated from adult esophageal surgery.

In the section on neuromuscular functional disorders, the chapter on the pharyngoesophageal region draws on the personal experience of the authors. Long-term manometric recordings are examined as an investigative tool and as a mean to establish a clearer diagnosis and an indication for treatment in this confusing area. The surgical philosophy of the authors is clearly defined in the chapter on achalasia.

Section 8 on hiatal hernia and reflux is extensive and covers all aspects of reflux disease. It is perfectly illustrated with meticulous description of the more frequently used abdominal and thoracic repairs. Emphasis is on objective staging and on standardized follow-up of at least 5 years. Pathology and indications are well reviewed but some views on obesity and reflux could certainly be challenged. The basic principles of surgical techniques are described, and detailed descriptions are limited to those operations with which the authors have experience. Recurrent reflux disease, reflux in childhood, and Barrett's esophagus are treated in separate chapters. In the following section on benign strictures, a certain amount of duplication is noted with the reflux section. Corrosive strictures are covered in a chapter referring to the Bristol experience.

In the section on esophageal neoplasms, the use of a simplified staging system is proposed, based mostly on wall penetration and node status. Informed consent is stressed as an important prerequisite to radical esophagectomy, an especially important attitude in these days of medical liability. The evaluation of palliative means besides surgery could have been more extensive. While sections 10 and 11 discuss trauma and esophageal varices, the final section looks at future developments in esophageal surgery.

This book is not an encyclopedic manual based on a worldwide bibliography. This is a legacy of precious information and knowledge gleaned from a lifetime experience with esophageal conditions. The style is frequently surprising, especially with its numerical descriptions of observations, indications, contraindications, theories, and so on. Their bias, admitted by the authors in their preface, is evident frequently. Many challenging opinions emphasize remaining areas of investigation and discussion in the field of esophageal surgery. This book focuses on the importance of objectivity in establishing standards of high quality care for all esophageal disorders. The opinions, the thinking, and the philosophy behind it are those of surgeons responsible for the formation and intellectual molding of two generations of surgeons in Europe, North America, and many countries around the world.

All surgeons involved in the management of esophageal disorders should have a copy of *Management of Esophageal Disease* in their libraries.

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Hernia, 3rd Ed. Lloyd M. Nyhus and Robert E. Condon. 620 pp. Philadelphia: J.B. Lippincott Co., 1989. $95.00.

A KEY TO THE ENJOYMENT and complete understanding of the first 310 pages (devoted to groin hernias) of this excellent monograph resides in comprehensive reading of the chapters on the anatomy of the inguinal region and on the theoretic aspects of hernia. Based on 185 personal dissections, Dr. Condon challenges some old anatomic concepts that have been cited as traditional fact in standard texts.

Although the basic format of the book remains much the same as the original edition published some 25 years ago, with historical quotes, chapters by national and international authorities, succeeded by guest commentary and editorial discussion, there is a freshness to this edition *via* the contributions of 58 new authors. New chapters abound, as do updated revisions of techniques and concepts. Even though the use of bio and prosthetic materials in the repair of hernias is adequately presented, most contributors stress the use of existing anatomic structures for repair and in so doing place the apparent current wave of enthusiasm for prosthetic-enhanced repair in proper perspective.

For those whose interests reside in esophageal reflux, this monograph provides 110 pages of comprehensive discussion regarding its etiology and treatment, including an excellent discussion of esophageal reflux in children. The presentations of rare and unusual hernias ensure the use of this monograph as a ready reference. In the current litigious climate, the chapter on the medical–legal aspects of hernia is appropriate not only for those surgeons who are particularly interested in hernia repair but also for all practicing surgeons because the principles discussed have broad application potential in the arena of medical liability.

This monograph is superbly written and edited. It is updated, comprehensive, and free of significant deficiencies and is recommended as a valuable addition to any surgical library. Certainly a copy of this new edition should be in the library of every program that trains general surgeons.

ARLIE R. MANSBERGER, JR., M.D.
Augusta, Georgia

Atlas of Duplex Scanning: Cartoid Arteries. John J. Cranley, Jr., William S. Karkow, and E. Douglas Baldridge. 358 pp. Philadelphia: W.B. Saunders, 1989. $125.00.

THIS HANDSOME ATLAS contains 173 high-quality B-mode ultrasound images of the cervical carotid artery bifurcation. Beneath each photograph, on the same page, is a color line drawing depicting the details shown in the B-mode image. On the opposite page, facing this plate, is a succinct description of the pictures, and when appropriate, a concise summary of the clinical problem.

Details seen in the B-mode images are expertly and meticulously described. Moreover methods of measuring the artery diameters and the degrees of stenosis caused by atherosclerosis are presented. Changes in the artery seen after surgery are also shown. Finally artifacts and technical problems that alter the images are identified and illustrated.

Because the atlas is primarily a personal, although expert, appraisal of the method, there are no references cited. There is, however, an excellent index to help the reader locate specific entities.

The main target of this work is, apparently, those people new to the area of ultrasound imaging. In the preface the other arm of the Duplex method, sound spectral analysis, is placed in a secondary role. Others in this field might disagree about the relative importance of the two modalities, but the authors of this book do suggest that both be used in concert. This atlas will be a valuable reference, especially for those entering the field. Even experienced technologists can benefit from a careful study of these B-mode images.

MALCOLM O. PERRY, M.D.
Nashville, Tennessee

Principles of Cardiac Arrhythmias, 4th Ed. Edward K. Chung. 835 pp. Baltimore: Williams & Wilkins, 1989. $119.95.

ALL SURGEONS SHOULD have a basic understanding of arrhythmias. They are a frequent occurrence after both cardiac and noncardiac operations, complicating up to 50% of surgical procedures. Most of these arrhythmias are benign but some are potentially life threatening and contribute significantly to patient morbidity and mortality. Proper management requires a knowledge of the predisposing medical and surgical factors and a familiarity with their diagnosis and treatment.

Principles of Cardiac Arrhythmias is in its fourth edition and represents a voluminous compilation of information regarding cardiac arrhythmias. The stated aim of this book is to provide the clinician with a practical approach to arrhythmias with numerous clinical applications and an in-depth discussion of the mechanisms responsible for various arrhythmias. There is a particular emphasis placed on the interpretation of the electrocardiogram, with many illustrative examples provided throughout the text.

In the 29 chapters there are sections dealing with all known disturbances of cardiac rhythm, their diagnosis, and treatment. Two chapters, Electrophysiologic Studies and Antiarrhythmic Drug Therapy, have been significantly revised and improved since the third edition. They are well written and represent excellent reviews of these areas. However this volume does have its shortcomings. Most of the chapters have not been significantly revised since the third edition in 1983. Because of the rapid advances in this field, some of the text and references are quite outdated. The section on mechanisms of arrhythmias is inadequate and contains no discussion of afterdepolarizations or the various models of reentry. The chapter on artificial cardiac pacing contains no reference to the new generation of sensor-driven, rated-modulated pacemakers. There is also no mention of the various antitachycardia devices that are being developed. In the chapter on direct current shock, the discussion of the automatic implantable cardioverter–defibrillator provides the reader with no reference more recent than 1981, despite the significant basic and clinical research on defibrillation in the last 5 years. Finally the book almost completely ignores the advances in the nonpharmacologic treatment of arrhythmias that have revolutionized the field in the last 10 years.

In conclusion this book has not been revised significantly since its third edition and does not include many of the recent advances in the understanding and treatment of cardiac arrhythmias. This book is too detailed for most practicing surgeons and is of little use to surgical housestaff officers because of its size and lack of discussion of current treatment modalities. However it does remain a well-written reference text with numerous electrocardiographic illustrations for those with a special interest in the clinical diagnosis of cardiac arrhythmias.

RALPH J. DAMIANO, JR., M.D.
Richmond, Virginia

Surgery for the Morbidly Obese Patient. Mervyn Deitel. 400 pp. Philadelphia: Lea & Febiger. 1989. $70.00.

MORBID OBESITY IS an increasingly common and serious disease that probably afflicts more than 5 million Americans. Many of these individuals are disabled not only by their size but also by the effects of the associated diseases: diabetes, hypertension, biliary disease, arthritis, and cardiopulmonary failure. Early deaths, often unexplained, are common.

Surgery has become accepted as the therapy of choice because it is the only measure that produces significant weight loss. Everything else has failed. In morbidly obese people diets produce insignificant weight loss; anoretic agents are dangerous, and the wiring of teeth, although initially effective, is followed by rapid regaining of weight when the braces are removed. In addition to the weight control, the bariatric operations also ameliorate diabetes, lower the blood pressure in many patients, and restore many to functional effectiveness. Unfortunately the operations are also associated with a significant rate of early and late complications, including staple line breakdowns and recurrent weight gain.

In *Surgery for the Morbidly Obese*, Mervyn Deitel offers a readable collection of articles that review (1) the basic principles of obesity, (2) the various operations for morbid obesity, and (3) several aspects of perioperative care and long-term management of those who have undergone bariatric surgery.

Deitel correctly cautions the reader that bariatric surgery, although no longer experimental, is still in its developmental stages. His review of the different operations, ranging from intestinal bypass to vertical banded gastroplasty, provides the best surgical history of the surgical battle to conquer obesity in print today. The collection is complete, the illustrations are, for the most part, clear, and the bibliography is comprehensive. The message is clear: we need far better information to evaluate the effectiveness of bariatric surgery. It is difficult to compare procedures in the face of incomplete follow-up and inadequate long-term data.

The book is somewhat uneven in its writing and editing. It could have been considerably stronger with an equally eclectic review of the physiology, the epidemiology, and socioeconomic consequences of obesity, as well as the long-term results of bariatric surgery.

In summary the book will serve as a useful reference for those interested in the history of bariatric surgery. The book should also stimulate a new cadre of surgeons and investigators to develop better therapeutic approaches for this severely debilitating disease.

WALTER J. PORIES, M.D.
Greenville, North Carolina

Pulmonary Vascular Physiology and Pathophysiology, Vol. 38 in the series **Lung Biology in Health and Disease.** E. Kenneth Weir and John T. Reeves. 744 pp. New York: Marcel Dekker, 1989. $125.00.

PULMONARY VASCULAR PHYSIOLOGY AND PATHOPHYSIOLOGY is the 38th volume of the continuing series *Lung Biology in Health and Disease*, edited by Claude Lenfant of the National Institutes of Health. The present volume is edited by major figures in the field of pulmonary physiology who have chosen 38 contributors, each of whom have published original work on the subject. The text covers a broad spectrum of topics pertaining to pulmonary circulation under normal and pathologic circumstances.

Within its 762 pages the authors have provided an authoritative, in-depth treatise of numerous topics of interest. Beginning with an engaging discussion of phylogeny and how it might be invoked to explain the paradoxical dynamics of the pulmonary circulatory response to hypoxia and hypercarbia, the authors proceed with basic discussions of the known and unknown factors controlling pulmonary hemodynamics from the fetus to the adult. Succeeding chapters explore the physiologic modifications secondary to exercise, pregnancy, and extremes of altitude and barometric pressure. The second portion of the book focuses on the pathophysiology of the pulmonary system. These chapters explore in detail the mechanisms for the development of pulmonary hypertension and its effects on the cardiovascular system. The complex interplay between the eicosanoids, platelet-activating factor, and their influences on vascular tone and the eventual development of structural changes in the pulmonary arterioles is highlighted. The discussions do not include algorithmic therapeutic regimens for the treatment of such disorders, but rather provide a revealing look into basic mechanisms that must be understood to intelligently interpret and manage the clinical situation.

All chapters in the text are extensively referenced. The chapters are well organized with appropriate sub-headings that accentuate topics of interest. The numerous illustrations are primarily line drawings and graphs. Included are a number of photomicrographs and electron-micrographs that are reproduced with great clarity.

This text is an invaluable reference source. It is designed for sophisticated audiences and has information that should prove useful to both basic physiologists and clinicians. It challenges one to think critically about a topic of increasing interest and importance, and it distills an extensive volume of literature and affords the reader the satisfaction of knowledge and stimulation of thought.

JAMES M. DOUGLAS, JR., M.D.
Durham, North Carolina

Multiple Organ Failure, Vol. 3 in the monograph series **New Horizons.** David J. Bihari and Frank B. Cerra. 397 pp. Fullerton, California: Critical Care Medicine, 1989. $32.00.

MULTIPLE ORGAN FAILURE IS a joint endeavor of the North American and European Societies of Critical Care. It reflects the results of a joint meeting on this topic held in Brussels in March 1988. The topics are well organized and are presented by known authorities.

The topics covered are criteria for adequate oxygen transport (these are probably now inadequate relative to the gut and liver because of microcirculatory problems and oxygen-free radical damage). The topics include the role of the activated leukocyte system (polymorphonuclear, monocyte-macrophage, lymphocyte), directly or indirectly, in further tissue damage and organ failure by their output of cytokines, prostanoids, oxygen-free radicals, activated complement, and lysosomal enzymes, the question of what causes continued leukocyte activation (wound *versus* or plus gut origin bacteria and toxins), the response of the systemic body to tissue damage by acute-phase proteins, muscle protein breakdown, wound healing (sometimes with excessive fibrosis in the lung), and systemic support by source control, oxygen transport support, nutritional support (parenteral and enteral), and selective gut decontamination.

As an expert in the field, I found this book fascinating. All research seems to indicate that the activated leukocyte system is the primary agent in septic organ failures and that bacteria and their toxins act not directly but *via* the activated leukocyte system. In multiple organ failure the key question is what causes the continued activation of the leukocyte system that leads to death. Derivative questions are, then, is this activation controllable in any way, and how do we support the patient while the leukocyte system is activated. Clearly key elements in this support are total body oxygen transport support and systemic protein synthesis support (high protein with high branched chain and mixed but restricted calories [long-chain saturated and unsaturated fatty acids, medium-chain fatty acids, and glucose]). After achieving this generalized systemic support, we are now finding the need for support of the gut mucosa as a barrier (enteral feeding, glutamine, epidermal growth factor, vitamin A and probably C, oxygen-free radical scavengers, and fiber), the need for support of the commensal bacteria of the gut to prevent growth of pathogenic bacteria (careful use of broad-spectrum systemic antibiotics, no stomach alkalinization, and selective gut decontamination), the need to support rapidly multiplying cells by added glutamine and perhaps arginine, and the need for down regulation of the arachnidonic system (omega 3 fish oil). Stated somewhat differently we are now recognizing that these patients have not only their presently known problems but also gut and lung wounds to which the body responds. It seems probable that the gut wound drives leukocyte-system activation while the endotracheal tube permits bacterial access and the lung wound supports bacterial growth to create the pneumonias observed. There are even reasons to believe that most of the secondary infections observed have bacteria that come from the gut.

This is an excellent book that gives insight into many of the stated problems in the multiple organ failure patient. Its one failure is lack of consideration of the response of the immune system, although that topic is too large to be covered in this book.

JOHN R. BORDER, M.D.
Buffalo, New York

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ALL SURGICAL SPECIALTIES, North & South Carolina, Florida, Delaware, nationwide. **Dr. Len Goodman, P.O. Box 25786, Charlotte, NC 28229. 704-536-2527.**

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ASSISTANT AND ASSOCIATE PROFESSORS OF SURGERY—Morehouse Department of Surgery seeks full-time academic surgical oncologist, general surgeon, general surgeon/ENT, vascular surgeon. To develop surgical service at busy 900-plus bed county facility. Pioneering opportunity. Salary negotiable. For further information please forward Curriculum Vitae to **Department of Surgery, 35 Butler St., Suite 302, Atlanta, GA 30335. Phone: (404) 222-2610.**

PHYSICIAN'S ASSISTANTS—Academic Surgical Department seeks three qualified surgical physician's assistants to join growing surgical program. Clinical experience in busy county facility. Salary negotiable. For further information, contact **Administrative Secretary (404) 222-2610.** Send Curriculum Vitae to **Department of Surgery, Morehouse School of Medicine, 35 Butler St., Suite 302, Atlanta, GA 30335.**

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BE/BC SURGEON needed to join busy surgical practice in northern New England. General and vascular surgery with endoscopic experience preferred. Income guarantee/partnership. Reply **Box ANN11D, J. B. Lippincott Co., East Washington Square, Philadelphia, PA 19105.**

COLORADO PERMANENTE MEDICAL GROUP is an expanding multispecialty prepaid group practice caring for members of the Kaiser Foundation Health Plan. Position available immediately for BE/BC general surgeon to join existing eleven physician department. Competitive salary and benefits. Contact: **V. A. LaFleur, M.D., Associate Medical Director, Colorado Permanente Medical Group, P.C., 2045 Franklin Street, Denver, CO 80205, (303) 861-3263.** EOE.

DIRECTOR OF SURGICAL CRITICAL CARE: The Oregon Health Sciences University Department of Surgery is seeking a surgeon to direct surgical critical care. The individual selected will additionally attend on the Trauma Service and be expected to develop a research program. It is anticipated that the applicant will be at the Assistant Professor level. Applicants should be Board Certified or Eligible in General Surgery and Critical Care. Reply with CV to: **Richard A. Crass, M.D., Professor and Head, Division of General Surgery, The Oregon Health Sciences University, L223A, 3181 S.W. Sam Jackson Park Road, Portland, Oregon 97201-3098.** The Oregon Health Sciences University is an equal opportunity/affirmative action employer.

DIRECTOR OF SURGICAL RESEARCH: The Mary Imogene Bassett Hospital, affiliated with Columbia University, is seeking an academic general surgeon or general surgeon/subspecialist with research experience to expand the surgical research program, conduct laboratory research, and supervise surgical resident research projects. Adequate space and initial support are available. Responsibilities will be divided evenly between clinical activities and The Mary Imogene Bassett Research Institute. Submit inquiries and CV to **Michael S. Gold, M.D., Surgeon-in-Chief, The Mary Imogene Bassett Hospital, Atwell Road, Cooperstown, NY 13326. Telephone (607) 547-3968.**

EMCO FELLOWSHIP: Clinical and Research Fellowship in Pediatric Extracorporeal Membrane Oxygenation and Surgical Intensive Care available for 1 to 2 years. Three years of general surgery training required. Send Curriculum vitae and three letters of reference to: **W. Hardy Hendren, M.D., Department of Surgery, Fegan 3, The Children's Hospital, 300 Longwood Avenue, Boston, MA 02115.**

FELLOWSHIP - G.I. Surgery — Ohio Digestive Disease Institute: Opportunity for additional training in surgery of liver, biliary tract, pancreas, esophagus, stomach, and colon for board eligible general surgeon. Rotation through active G.I. diagnostic and procedure laboratory includes endoscopy, colonoscopy, ERCP, gastric analysis, and manometry and motility testing. Exposure to laboratory research as desired. For further information contact: **E. Christopher Ellison, M.D., Ohio Digestive Disease Institute, Grant Medical Center, 111 S. Grant Ave., Columbus, OH 43215.**

GENERAL and NON-CARDIAC THORACIC SURGERY BE/BC to join multispecialty group located in a modern city nestled amongst the picturesque Blue Ridge Mountains of Virginia. There are numerous recreational opportunities summer and winter. The group practices primarily at two acute care facilities, both with trauma center designation. The group includes two vascular and one thoracic surgeon plus eight other general and specialty surgeons. Bonus at sign-up if no recruiting firm involved. Apply to **Box ANN11E, J. B. Lippincott Company, East Washington Square, Philadelphia, PA 19105.**

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GENERAL SURGEON needed to join four General Surgeons at a major regional multispecialty clinic in Billings, Montana. Four university trained surgeons seek an associate with exemplary training. Training, experience, or interest in oncology is desirable. The General Surgery Department at the Billings Clinic provides services in General, thoracic and vascular surgery and receives referrals from a broad area for treatment of critical care, emergency, and gastrointestinal disease. The clinic setting includes all specialties and is adjacent to an outstanding tertiary care referral hospital. Excellent opportunity for top notch board eligible or board certified general surgeon looking for a challenging practice in a geographic area offering unlimited recreational potential. Those interested, please send CV to **John W. Heizer, M.D., Medical Director, The Billings Clinic, P.O. Box 35100, Billings, Montana 59107-5100.**

GENERAL/VASCULAR SURGEON with vascular fellowship to join three surgeons in practice of General, Vascular and Thoracic Surgery in Southern New Jersey, close to Philadelphia and shore points. Benefits and salary leading to partnership opportunity. Send CV to **Box ANN11B, J. B. Lippincott Company, East Washington Square, Philadelphia, PA 19105.**

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RESEARCH FELLOWSHIP: Research Fellowship in thoracic oncology available for two to three years. Projects include the immunology and molecular biology of lung cancer and studies on molecular mechanisms of lung cancer progression. Salary is supported by an NIH Training Grant. Applicants must be U.S. Citizens or permanent residents enrolled in a General or Thoracic Surgery Residency Program. Send curriculum vitae and three references to **Dr. Jack A. Roth, Chairman, Department of Thoracic Surgery, Box 109, University of Texas M.D., Anderson Hospital and Tumor Institute, 1515 Holcombe Blvd., Houston, Texas 77030.** An Equal Opportunity/Affirmative Action Employer.

THORACIC SURGEON: A 220-physician multispecialty prepaid group in Hawaii is seeking a qualified M.D. to accept the second thoracic surgery position. Must be experienced in adult cardiac, general thoracic and peripheral vascular surgery. Excellent fringe benefits. Malpractice paid. Please direct curriculum vitae to: **Hawaii Permanente Medical Group, Inc., 3288 Moanalua Road, Honolulu, HI 96819.** (An Equal Opportunity Employer.)

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TRAUMA DIRECTOR & ASSISTANT DIRECTOR OF SURGERY: San Joaquin General Hospital, a university affiliated teaching hospital, seeks a Trauma Surgeon to direct trauma program development. In addition, the individual would serve as Assistant Director of Surgery for the Surgery Residency Program. Applicants must be Board Certified or Board Eligible. Vascular Surgery training or experience would be beneficial. Responsibilities include patient care, teaching surgical residents and administration. Excellent financial package. Send all inquiries and CV to: **Nathan M. Matolo, M.D., Chairman, Department of Surgery, San Joaquin General Hospital, P.O. Box 1020, Stockton, CA 95201, (209) 468-6600.** San Joaquin General Hospital is an Affirmative Action/Equal Opportunity Employer.

TRAUMA FELLOWSHIP: Eastern Virginia Medical School, Department of Surgery, Division of Trauma/Critical Care—The Department of Surgery of Eastern Virginia Medical School and the Shock Trauma Center/Sentara Norfolk General Hospital are accepting applications for a one year Trauma and Critical Care Fellowship commencing July 1, 1990. Applicants must have completed a residency program in General Surgery with education and experience in the field of Trauma/Critical Care. Applicants must be Board certified or eligible. The fellowship will be based at Sentara Norfolk General Hospital, the designated Level I adult/pediatric regional trauma and burn facility which has approximately 1,700 trauma/burn admissions per year. The one year program will provide significant operative and critical care experience along with an opportunity for involvement with ongoing clinical research. Applicants should send a letter of application, curriculum vitae and the names of three references to: **L.D. Britt, M.D., M.P.H., Chief, Division of Trauma and Critical Care, Eastern Virginia Medical School, Medical Director, Shock Trauma Center, Sentara Norfolk General Hospital, 825 Fairfax Avenue, Norfolk, VA 23507.**

UCLA School of Medicine, Chief of Trauma and Surgical Critical Care: The UCLA School of Medicine is recruiting a board certified general surgeon to be Chief of Trauma and Surgical Critical Care. The UCLA Medical Center is a 711-bed, level 1 tertiary care center. The individual will direct the trauma service and coordinate critical care activities in the Department of Surgery. These activities would include the development of a critical care teaching program. The candidate will have a faculty appointment and be expected to contribute to all academic programs in the Department of Surgery. Interested applicants should submit their curriculum vitae to **Dr. Michael Zinner, Chairman, Department of Surgery, UCLA School of Medicine, 10833 LeConte Street, Los Angeles, CA 90024.**

VASCULAR ASSOCIATE: Multi-specialty surgical group in Philadelphia suburbs seeking a Vascular Associate. Must be BC/BE—prefer Fellow finishing now or recent graduate. Excellent benefits. Eventual partnership. Send reply to: **Vicki Robbins, Surgical Services, Ltd., Moss Plaza, 8892 Bustleton Ave., Suite 206, Philadelphia, PA 19115.**

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WANTED: Board eligible or Board certified general surgeon with subspecialty in vascular surgery to join a three man surgical practice in Upstate New York. Send C.V. to **Surgical Associates, P.C., 161 Riverside Drive, Binghamton, NY 13905.**

Miscellaneous

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Postgraduate Course: "The California Trauma Conference" in San Francisco, California on November 30-December 2, 1989. The course directors are Frank R. Lewis, M.D., A. Brent Eastman, M.D. and James Holcroft, M.D. Please call **Bob Steele at 415-821-8814 for additional information.**

April 20-21, 1990: Vascular Trauma: Diagnosis and Management—Postgraduate course, sponsored by Department of Surgery, University of Florida Health Science Center, Jacksonville, Florida and the Florida Vascular Society, at the Jekyll Island Club Hotel, Jekyll Island, Georgia. For information contact **Alicia Azouz, CME Coordinator, UFHC/J, 580 W. 8th Street, Jacksonville, Florida 32209, (904) 359-6510.**

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SCLEROTHERAPY FOR TRUNCAL VARICOSE VEINS AND TELANGIECTASIAS: PRACTITIONER'S GUIDE ($55) available from Vein Disorders Center, 16311 Ventura Blvd., Suite 505, Encino, CA 91436; (818) 905-5502; FAX (818) 905-6092.

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ONCOLOGY FELLOWSHIPS AT NIH

The National Cancer Institute, National Institutes of Health, Public Health Service is accepting applications for fellowships in oncology. Positions are available to physicians who have completed at least two years of training in internal medicine, pediatrics, or surgery.

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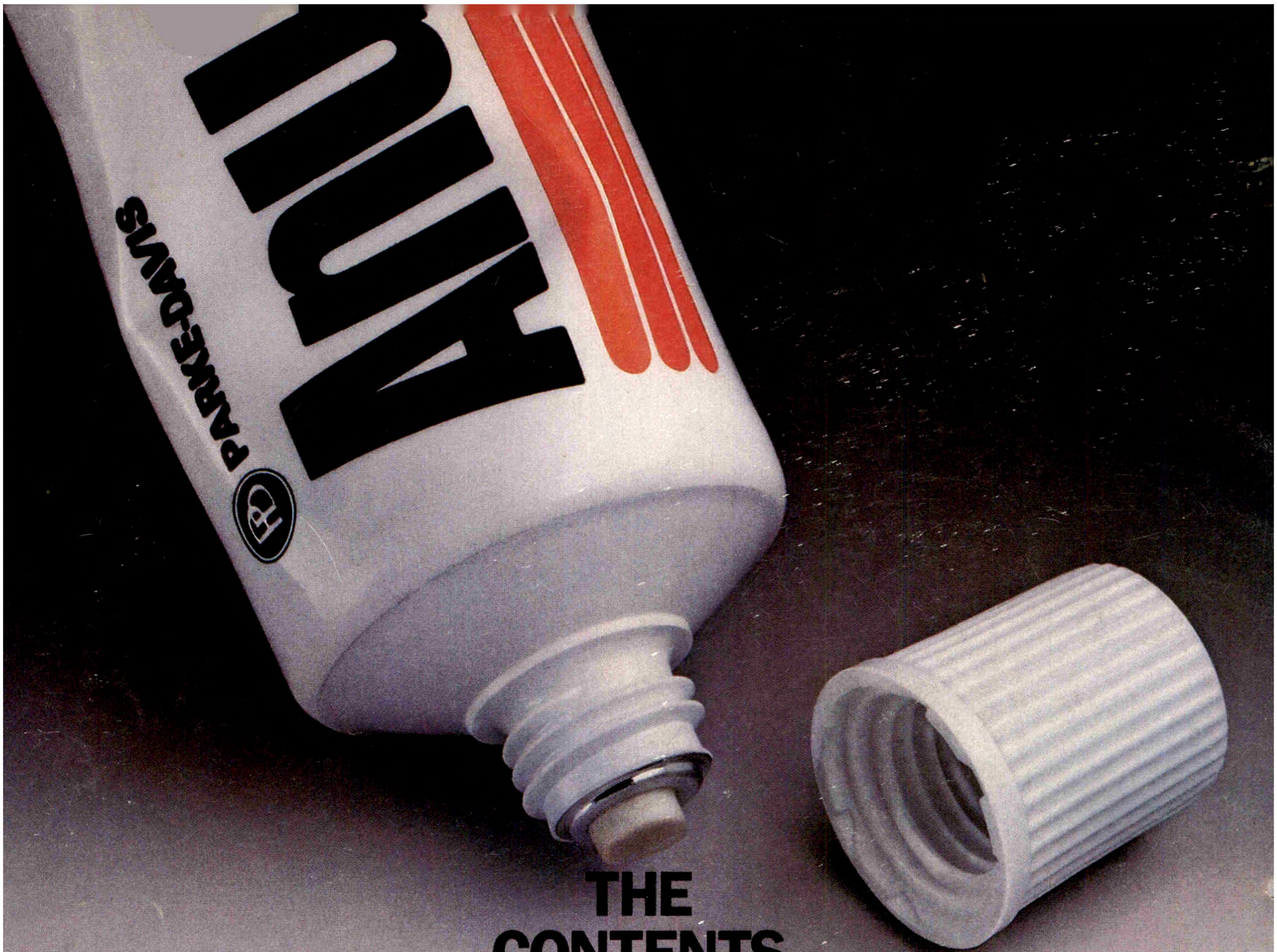

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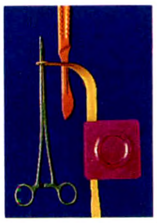

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In intra-abdominal and gynecologic infection due to indicated organisms

References: **1.** Nightingale CH, Smith KS, Quintiliani R, et al: The conversion of cefoxitin usage to cefotetan: An interdisciplinary approach. *Am J Surg* 1988;155(5A):101-102. **2.** Sochalski A, Sullman S, Andriole VT: Cost-effectiveness study of cefotetan versus cefoxitin and cefotetan versus combination antibiotic regimens. *Am J Surg* 1988;155(5A):96-101. **3.** CEFOTAN® (cefotetan disodium) full prescribing information issued March 1986. **4.** *Physicians' Desk Reference*, ed 43. Oradell, NJ, Medical Economics Co, 1989. Mefoxin® (cefoxitin sodium, MSD), pp 1355-1357. **5.** Carver M, Quintiliani R, Nightingale CH: Comparative pharmacokinetic study of cefotetan and cefoxitin in healthy volunteers. *Infect Surg*, April 1986 (suppl), pp 11-14. **6.** Quintiliani R, Nightingale CH, Stevens RC, et al: Comparative pharmacokinetics of cefotetan and cefoxitin in patients undergoing hysterectomies and colorectal operations. *Am J Surg* 1988;155(5A):67-70.

Please see adjacent page for brief summary of prescribing information.

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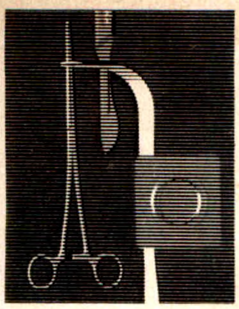

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In intra-abdominal and gynecologic infection due to indicated organisms

For Intravenous or Intramuscular Use
BRIEF SUMMARY

INDICATIONS AND USAGE

TREATMENT: CEFOTAN® (cefotetan disodium) is indicated for the therapeutic treatment of the following infections when caused by susceptible strains of the designated organisms:

Urinary tract infections caused by *E coli, Klebsiella* species (including *K pneumoniae*), *Proteus mirabilis* and *Proteus* sp (which may include the organisms now called *Proteus vulgaris, Providencia rettgeri*, and *Morganella morganii*).

Lower respiratory tract infections caused by *Streptococcus pneumoniae* (formerly *D pneumoniae*), *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Haemophilus influenzae* (including ampicillin-resistant strains), *Klebsiella* species (including *K pneumoniae*), and *E coli.*

Skin and skin structure infections caused by *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis, Streptococcus pyogenes* and *Streptococcus* species (excluding enterococci), and *E coli.*

Gynecologic infections caused by *Staphylococcus aureus** (including penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis, Streptococcus* species (excluding enterococci), *E coli, Proteus mirabilis, Neisseria gonorrhoeae, Bacteroides* species (excluding *B distasonis, B ovatus, B thetaiotaomicron*), *Fusobacterium* species,* and gram-positive anaerobic cocci (including *Peptococcus* and *Peptostreptococcus* species*).

Intra-abdominal infections caused by *E coli, Klebsiella* species (including *K pneumoniae**), *Streptococcus* species (excluding enterococci), and *Bacteroides* species (excluding *B distasonis, B ovatus, B thetaiotaomicron*).

Bone and joint infections caused by *Staphylococcus aureus.**

*Efficacy for this organism in this organ system was studied in fewer than ten infections.

Specimens for bacteriological examination should be obtained in order to isolate and identify causative organisms and to determine their susceptibilities to cefotetan. Therapy may be instituted before results of susceptibility studies are known; however, once these results become available, the antibiotic treatment should be adjusted accordingly.

In cases of confirmed or suspected gram-positive or gram-negative sepsis or in patients with other serious infections in which the causative organism has not been identified, it is possible to use CEFOTAN concomitantly with an aminoglycoside. Cefotetan combinations with aminoglycosides have been shown to be synergistic in vitro against many Enterobacteriaceae and also some other gram-negative bacteria. The dosage recommended in the labeling of both antibiotics may be given and depends on the severity of the infection and the patient's condition.

NOTE: If CEFOTAN and an aminoglycoside are used concomitantly, renal function should be carefully monitored, especially if higher dosages of the aminoglycoside are to be administered or if therapy is prolonged, because of the potential nephrotoxicity and ototoxicity of aminoglycosidic antibiotics. Although, to date, nephrotoxicity has not been noted when CEFOTAN was given alone, it is possible that nephrotoxicity may be potentiated if CEFOTAN is used concomitantly with an aminoglycoside.

PROPHYLAXIS: The preoperative administration of CEFOTAN may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures that are classified as clean contaminated or potentially contaminated (eg, cesarean section, abdominal or vaginal hysterectomy, transurethral surgery, biliary tract surgery, and gastrointestinal surgery).

The prophylactic dose of CEFOTAN should be administered 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, CEFOTAN should be administered intravenously after the clamping of the umbilical cord.

If there are signs and symptoms of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate therapeutic measures may be initiated.

CONTRAINDICATIONS

CEFOTAN is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS

Before therapy with CEFOTAN is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefotetan disodium, cephalosporins, penicillins, or other drugs. This product should be given cautiously to penicillin-sensitive patients. Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. If an allergic reaction to CEFOTAN occurs, discontinue the drug. Serious acute hypersensitivity reactions may require epinephrine and other emergency measures.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad-spectrum antibiotics may alter normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin in vitro.

Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated. When the colitis is not relieved by drug discontinuance, or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile*. Other causes should also be considered.

PRECAUTIONS

GENERAL: As with other broad-spectrum antibiotics, prolonged use of CEFOTAN may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection does occur during therapy, appropriate measures should be taken.

In common with many other broad-spectrum antibiotics, CEFOTAN may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment or poor nutritional state, the elderly and patients with cancer. Prothrombin times should be monitored in patients at risk and exogenous vitamin K administered as indicated.

CEFOTAN should be used with caution in individuals with a history of gastrointestinal disease, particularly colitis.

INFORMATION FOR PATIENTS: As with some other cephalosporins, a disulfiram-like reaction characterized by flushing, sweating, headache, and tachycardia may occur when alcohol (beer, wine, etc.) is ingested within 72 hours after CEFOTAN administration. Patients should be cautioned about the ingestion of alcoholic beverages following the administration of CEFOTAN.

DRUG INTERACTIONS: Although to date nephrotoxicity has not been noted when CEFOTAN was given alone, it is possible that nephrotoxicity may be potentiated if CEFOTAN is used concomitantly with an aminoglycoside.

DRUG/LABORATORY TEST INTERACTIONS: A false positive reaction for glucose in urine may occur with Benedict's or Fehling's solution.

As with other cephalosporins, high concentrations of cefotetan may interfere with measurement of serum and urine creatinine levels by Jaffe reaction and produce false increases in the levels of creatinine reported.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Although long-term studies in animals have not been performed to evaluate carcinogenic potential, no mutagenic potential of cefotetan was found in standard laboratory tests.

Cefotetan has adverse effects on the testes of prepubertal rats. Subcutaneous administration of 500 mg/kg/day (approximately 8-16 times the usual adult human dose) on days 6-35 of life (thought to be

CEFOTAN® (cefotetan disodium)

developmentally analogous to late childhood and prepuberty in humans) resulted in reduced testicular weight and seminiferous tubule degeneration in 10 of 10 animals. Affected cells included spermatogonia and spermatocytes; Sertoli and Leydig cells were unaffected. Incidence and severity of lesions were dose-dependent; at 120 mg/kg/day (approximately 2-4 times the usual human dose) only 1 of 10 treated animals was affected, and the degree of degeneration was mild.

Similar lesions have been observed in experiments of comparable design with other methylthiotetrazole-containing antibiotics and impaired fertility has been reported, particularly at high dose levels. No testicular effects were observed in 7-week-old rats treated with up to 1000 mg/kg/day SC for 5 weeks, or in infant dogs (3 weeks old) that received up to 300 mg/kg/day IV for 5 weeks. The relevance of these findings to humans is unknown.

USAGE IN PREGNANCY: Pregnancy Category B: Reproduction studies have been performed in rats and monkeys at doses up to 20 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefotetan. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

USAGE IN NURSING MOTHERS: Cefotetan is excreted in human milk in very low concentrations. Caution should be exercised when cefotetan is administered to a nursing woman.

PEDIATRIC USE: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

In clinical studies, the following adverse effects were considered related to CEFOTAN therapy.

Gastrointestinal symptoms occurred in 1.5% of patients; the most frequent were diarrhea (1 in 80) and nausea (1 in 700).

Hematologic laboratory abnormalities occurred in 1.4% of patients and included eosinophilia (1 in 200), positive direct Coombs' test (1 in 250), and thrombocytosis (1 in 300).

Hepatic enzyme elevations occurred in 1.2% of patients and included a rise in SGPT (1 in 150), SGOT (1 in 300), alkaline phosphatase (1 in 700), and LDH (1 in 700).

Hypersensitivity reactions were reported in 1.2% of patients and included rash (1 in 150) and itching (1 in 700).

Local effects were reported in less than 1.0% of patients and included phlebitis at the site of injection (1 in 300), and discomfort (1 in 500). During postmarketing experience with CEFOTAN, anaphylactic reactions and transient thrombocytopenia have been reported.

DOSAGE AND ADMINISTRATION

TREATMENT: The usual adult dosage is 1 or 2 grams of CEFOTAN administered intravenously or intramuscularly every 12 hours for 5 to 10 days. Proper dosage and route of administration should be determined by the condition of the patient, severity of the infection, and susceptibility of the causative organism.

GENERAL GUIDELINES FOR DOSAGE OF CEFOTAN

Type of Infection	Daily Dose	Frequency and Route
Urinary Tract	1-4 grams	500 mg every 12 hours IV or IM 1 or 2 g every 24 hours IV or IM 1 or 2 g every 12 hours IV or IM
Other Sites	2-4 grams	1 or 2 g every 12 hours IV or IM
Severe	4 grams	2 g every 12 hours IV
Life-Threatening	6* grams	3 g every 12 hours IV

*Maximum daily dosage should not exceed 6 grams.

PROPHYLAXIS: To prevent postoperative infection in clean contaminated or potentially contaminated surgery in adults, the recommended dosage is 1 or 2 g of CEFOTAN administered once, intravenously, 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, the dose should be administered as soon as the umbilical cord is clamped.

IMPAIRED RENAL FUNCTION: When renal function is impaired, a reduced dosage schedule must be employed. The following dosage guidelines may be used.

DOSAGE GUIDELINES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

Creatinine Clearance mL/min	Dose	Frequency
>30	Usual Recommended Dosage*	Every 12 hours
10-30	Usual Recommended Dosage*	Every 24 hours
<10	Usual Recommended Dosage*	Every 48 hours

*Dose determined by the type and severity of infection, and susceptibility of the causative organism.

Alternatively, the dosing interval may remain constant at 12 hour intervals, but the dose reduced to one-half the usual recommended dose for patients with a creatinine clearance of 10-30 mL/min, and one-quarter the usual recommended dose for patients with a creatinine clearance of less than 10 mL/min.

When only serum creatinine levels are available, creatinine clearance may be calculated from the following formula. The serum creatinine level should represent a steady state of renal function.

$$\text{Males:} \quad \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/100 mL)}}$$

$$\text{Females:} \quad 0.9 \times \text{value for males}$$

Cefotetan is dialyzable and it is recommended that for patients undergoing intermittent hemodialysis, one-quarter of the usual recommended dose be given every 24 hours on days between dialysis and one-half the usual recommended dose on the day of dialysis.

HOW SUPPLIED

CEFOTAN is a dry, white to pale yellow powder supplied in vials containing cefotetan disodium equivalent to 1 g and 2 g cefotetan activity for intravenous and intramuscular administration. The 1 g dose is available in 10 mL and 100 mL vials, and the 2 g dose is available in 20 mL and 100 mL vials. CEFOTAN is also available in a pharmacy bulk package of 10 g in 100 mL vials. The vials should not be stored at temperatures above 22°C and should be protected from light.

1 g in 10 mL vial (NDC 0038-0376-10); 2 g in 20 mL vial (NDC 0038-0377-20); 1 g in 100 mL vial (NDC 0038-0376-11); 2 g in 100 mL vial (NDC 0038-0377-21); 10 g in 100 mL vial (NDC 0038-0375-10).

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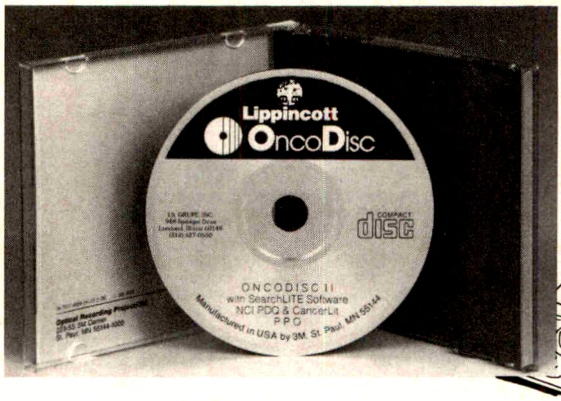

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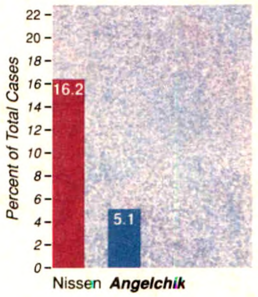

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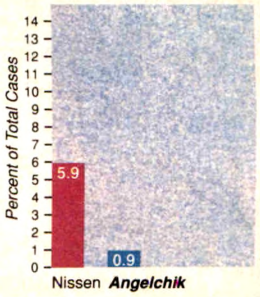

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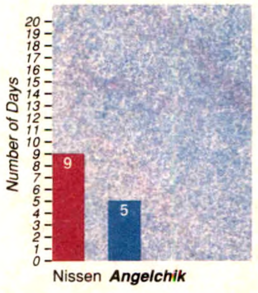

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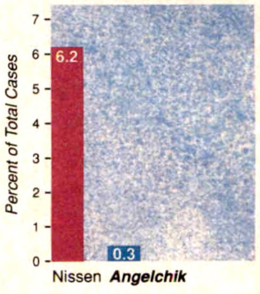

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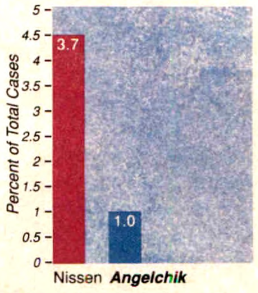

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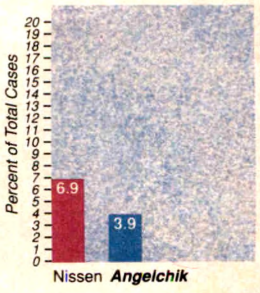

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Annals of Surgery

What's New In General Surgery

Current Diagnosis and Management of Zollinger–Ellison Syndrome

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The treatment of patients with Zollinger–Ellison syndrome (ZES) has undergone dramatic evolution during the past decade. Although initially regarded as an incurable tumor, resection of gastrinoma for potential cure has been reported in 30% to 40% of selected patients in recent series. Conversely, although definitive control of acid hypersecretion is achieved by total gastrectomy, histamine (H_2)-receptor antagonists and the newly introduced agents omeprazole and somatostatin analogues allow effective medical therapy of gastric acid overproduction. Confirmation of the diagnosis is best achieved with the I.V. secretin stimulation test, and tumor localization techniques are mandatory to identify candidates for operative tumor resection. Intraoperative sonography and careful exploration are required for tumor removal; successful tumor resection is associated with prolonged survival. The majority of patients (60%) are still found to have malignant disease at the time of diagnosis, but 10-year overall survival commonly exceeds 40%. The presence of multiple endocrine neoplasia type I (MEN-I) is seen in 10% to 25% of patients; correction of hypercalcemia alone may have therapeutic benefit in some ZES patients, and while gastrinoma resection is rarely possible, MEN-I patients demonstrate prolonged survival. The choice of medical rather than surgical therapy for acid hypersecretion depends on the suitability of each patient for careful and repeated endoscopic and chemical studies, *versus* the likelihood of a successful postoperative outcome. Socioeconomic, geographic, and related medical factors in each case may dictate the form of long-term antisecretory therapy. Exploration for possible tumor resection is indicated for virtually all patients who have no documented metastatic disease.

IT MAY BE SAID that the modern era of gastrointestinal endocrinology began at the 1955 meeting of the American Surgical Association with the description by Zollinger and Ellison of the syndrome that bears their names.[1] The association of peptic ulceration with a non-beta-cell adenoma of the pancreas brought clinical relevance to the physiologic studies reported 50 years previously by Edkins that identified an acid secretory hormone named gastrin.[2] Although the pathologic significance of hypergastrinemia was suggested by the syndrome's original description, pathophysiologic proof was not found until 1960 when Gregory et al.[3,4] in London successfully isolated the gastrin peptide from a tumor resected by Stammers from a patient in Birmingham, England. After the chemical isolation and structural identification of gastrin, radioimmunoassay techniques were perfected that allowed the definitive diagnosis of the gastrinoma syndrome.[5,6]

Gastrin-producing tumors are rare; about 0.1% of all cases of peptic ulcer disease are associated with gastri-

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noma. Because of the decline over the past two decades in the number of patients requiring surgery for peptic ulcer disease, however, the relative importance of gastrinoma in the surgical management of ulcer diastheses has increased. The frequency of the gastrinoma syndrome among ulcer patients seen on a university surgical service now approaches 2% to 5% in many centers. This syndrome has therefore aroused continued interest among surgeons and gastroenterologists. Although the patient with a positive diagnosis of Zollinger–Ellison Syndrome (ZES) usually can be managed successfully, the failure to appreciate the presence of a gastrinoma, or the maintenance of insufficient or inappropriate antisecretory therapy, can lead to severe morbidity or death in these patients.

Beyond those issues related to the care of patients with ZES, the study of gastrinomas has also led to major advances in the understanding of the physiology of gastrin, including both its acid secretory function as well as its trophic properties. In addition, gastrinoma has served as an important tumor model that may be either familial or sporadic. The nature of functioning hormone-producing neoplasms and the biology of pleuripotential or polyclonal tumors with the capacity to synthesize multiple functional peptides has been appreciated through investigation of gastrinomas. Recent advances in the technical development of methods for pancreatic tumor localization have been inspired by and tested in patients with ZES. The importance and influence of gastrinomas therefore extends far beyond the rare syndrome itself, and has influenced our general understanding of ulcer disease and tumor biology, as well as technical developments relevant to pancreatic and gastric surgery.

The management of patients with ZES has been a focus of controversy and evolution during the past few years. With the introduction of more potent antisecretory drugs, an increased use of long-term medical management of acid hypersecretion has resulted in a decrease in the number of patients treated with total gastrectomy for definitive control of ulcer disease. In contrast the role of surgery in the care of the patient's underlying lesion has increased and the importance of performing a curative resection has become more widely appreciated. Although regarded until this decade as a virtually incurable tumor with a risk of mortality largely secondary to the complications of ulcer disease, it is now believed to be a potentially curable neoplasm manifested by acid hypersecretion that can nonetheless be managed successfully with judicious use of medical or surgical treatment.

Clinical Presentation and Pathologic Findings

Demographics

Gastrinoma comprises the second-most commonly reported islet-cell tumor,[7,8] although many centers find that gastrinomas are more frequently diagnosed than any other islet-cell neoplasm. Patients represent the entire adult age span, from the second to the eighth decades of life. There is a slight preponderance of males among reported cases, and the distribution of the syndrome is worldwide. Patients represent all socioeconomic groups, and no particular racial, ethnic, religious, or cultural associations have been reported.[9] Because the diagnosis usually rests on the availability of appropriate gastrin measurements, reported cases are clustered in those cities or countries with readily available gastrin radioimmunoassay capability.

Symptomatology

Acid peptic disease and its complications usually account for the presenting symptoms in patients with gastrinoma. Dyspepsia, upper gastrointestinal tract bleeding, and ulcer perforation are common manifestations. Diarrhea or steatorrhea are also noted in as many as 40% of cases,[7] and typically produce a relatively low volume output believed to be secondary to high gastric secretion and intestinal mucosal sloughing secondary to acid hypersecretion. Esophageal symptoms are present in a minority of cases, with pyrosis or dysphagia secondary to peptic esophagitis.[10]

Weight loss and malnutrition are commonly associated with ZES, and may be the only symptoms in a small number of patients who demonstrate otherwise occult presentations of their illness. Most patients have a history of ulcer symptoms, although one third of patients have a history of suspected or proved ulcer that is deceptively unimpressive in intensity or duration. Frequently patients have had medical or surgical therapy for ulcer disease in the past, and many ZES patients have a history of multiple surgical procedures and intractable symptoms that ultimately lead to the ZES diagnosis. Finally an important clue to the presence of the gastrinoma is a positive family history of peptic ulcer disease, pancreatic tumor, or of symptoms referable to hypercalcemia and hyperparathyroidism.[11-13]

Pathology

The gastrinoma is a gastrin-cell, or G-cell, adenoma or adenocarcinoma. It is histologically characteristic of islet-cell tumors in general, with a uniform cuboidal pattern of cells with prominent nucleoli, modest cytoplasm, and few mitotic figures in either benign or malignant tumors. These tumors are usually malignant (60%), multifocal (60%), and may reside in the pancreas (70% to 90%), duodenal wall (15% to 20%), or in extraintestinal locations (5% to 15%) such as lymphatic tissue or the liver.[14,15] More than 90% of gastrinomas occur within the gastrinoma triangle, which is bounded by the third portion of the duodenum, the neck of the pancreas, and the porta hepatis.[16]

Pancreatic gastrinomas may be prominent, obvious lesions, but more frequently they are small (0.5 to 2.0 cm), multiple, intrapancreatic lesions. Duodenal gastrinomas are usually small intramural lesions that may be more prominent on either the mucosal or serosal side of the bowel wall (Fig. 1). Careful attention at endoscopy to the inner wall of the air-distended duodenum is important to detect small, mucosally oriented duodenal lesions. Although single or multiple discrete adenomas or adenocarcinomas are most common, diffuse hyperplasia of G cells throughout the pancreatic islets has also been described in association with this syndrome.[17] The presence of seeming lymphatic or hepatic "primaries" of gastrinoma has always been a troubling finding, and this unusual but consistent finding in a small number of cases has been suggested to represent isolated metastatic foci from a previously resected tumor. Because many patients have undergone previous gastric or duodenal operations, the inadvertent previous removal of a duodenal gastrinoma is a theoretical possibility in these cases.

The vast majority of gastrinomas are found in isolated, sporadic cases without other genetic association. Between 10% and 25% of gastrinomas appear as part of the Multiple Endocrine Neoplasia-Type I (MEN-I) Syndrome, and are associated with parathyroid, pituitary, and other pancreatic apudomas.[18] A small number of gastrinomas appear to be familial, without MEN-I manifestations, and a number of isolated gastrinoma kindreds have been identified.[7,9,15,19]

Diagnosis

Index of Suspicion

Although a majority of patients demonstrate advanced or intractable ulcer symptoms, one third of Zollinger–Ellison patients may otherwise resemble "garden-variety" peptic ulcer disease patients in their clinical presentation.[7,9,11,15,19] Adolescent or elderly patients who develop peptic ulcer disease are suspect for harboring ZES, and patients with positive family histories of gastrointestinal or endocrine illness are also likely candidates. The finding of enlarged gastric or duodenal mucosal folds in a patient with ulcer disease suggests ZES, and any patient with concurrent peptic ulcer and hypercalcemia is a strong candidate for gastrinoma as part of the MEN-I Syndrome. With the recent advent of routine intragastric pH monitoring and antacid prophylaxis in intensive care units throughout the hospital, patients with ZES are also being identified who demonstrate more than a 60-cc-per-hour antacid need while being treated for other illnesses. Unexplained, high-output, small bowel fistulae following upper abdominal surgery, and marginal ulceration soon after an otherwise unremarkable gastric operation, are also harbingers of an underlying gastrinoma. The successful identification of Zollinger–Ellison patients is directly related to a high index of suspicion, and the liberal use of routine blood studies to confirm the presence and etiology of hypergastrinemia.[20]

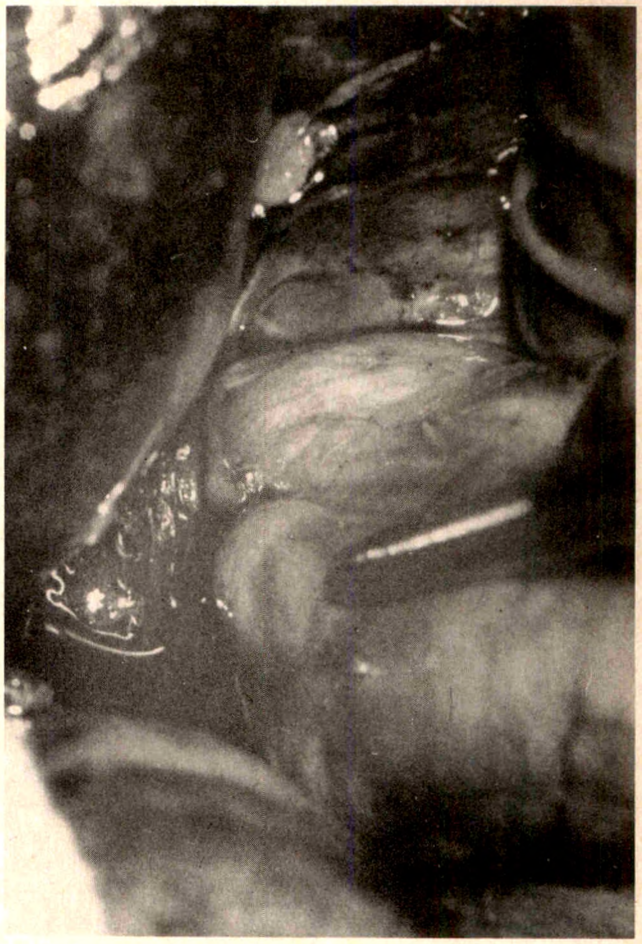


FIG. 1. Duodenal gastrinoma. Operative appearance of 1-cm intramural gastrinoma on lateral surface of duodenal C-loop. Lesion was resected without cure of hypergastrinemia.

Basal Chemical Studies

The majority of patients with ZES demonstrate fasting basal hypergastrinemia. Normal gastrin values vary from laboratory to laboratory, but basal gastrin levels less than 50 pg/mL (25 pM) are not likely to be associated with ZES. Basal gastrin levels between 100 and 1000 pg/mL are considered intermediate, and fasting levels greater than 1000 pg/mL are virtually diagnostic of the disease.[21]

Basal acid output (BAO) from the fasted stomach correlates directly with gastrin levels, and is also a good indicator of ZES when elevated. Although an untreated fasting value of less than 10 mEq/hour is considered normal, levels greater than 15 mEq/hour suggest ZES in nonoperated patients when accompanied by hypergastrinemia.[7,21] Unfortunately acid secretory studies cannot be performed within 48 to 72 hours of antisecretory therapy and may be hazardous in patients with active ulcer disease. They are also highly operator dependent, are prone to technical errors, and are uncomfortable for patients who do not otherwise require a nasogastric tube. Their usefulness is therefore considerably less than that of plasma gastrin analysis. In a previously nonoperated patient, a simple fasting intragastric pH value of 3 or more virtually excludes the diagnosis of ZES.[21]

Both basal gastrin and BAO are also influenced by previous ulcer surgery as well as medications. Any form of previous vagotomy, gastric distention, or therapy with H_2-receptor blockade are all associated with elevations in serum gastrin; previous antrectomy or subtotal gastrectomy should virtually abolish normal serum gastrin levels. Conversely vagotomy, gastrectomy, and antacid therapy may be expected to lower the BAO, while gastric distention and pain will increase the BAO. It is therefore crucial to ellicit an accurate history of previous gastric surgery from patients undergoing studies of gastric acid secretion. Modest elevations in serum gastrin are therefore nonspecific in patients with previous ulcer therapy, and may occur in cases of MEN-I syndrome as well (Table 1). Provocative tests designed to ellicit a diagnostic response from the gastrinoma are therefore invaluable to establish or confirm the diagnosis.

The most widely used stimulation test is the secretin test in which secretin (2 U/kg) is given by intravenous bolus injection after two or three basal samples are obtained.[6,22] It is crucial to obtain blood samples at the two- and five-minute time points after this secretin infusion, because the diagnostic twofold or greater rise (or 200 pg/mL increment) in serum gastrin may occur only at one of these sample times (Fig. 2). Samples are obtained at ten-minute intervals thereafter until 30 minutes, at which time the test is concluded. The ease and simplicity of the secretin stimulation test make it readily useful in any clinical setting, and its use should not be overlooked in any case suggestive of ZES or in patients in whom basal gastrin levels are nondiagnostic. Care must be taken during sample collection and handling because heparin may interfere with some gastrin assays. The secretin test is safe to perform, however, even in the setting of active ulcer disease, because the duration of the provoked gastrin response is very brief.

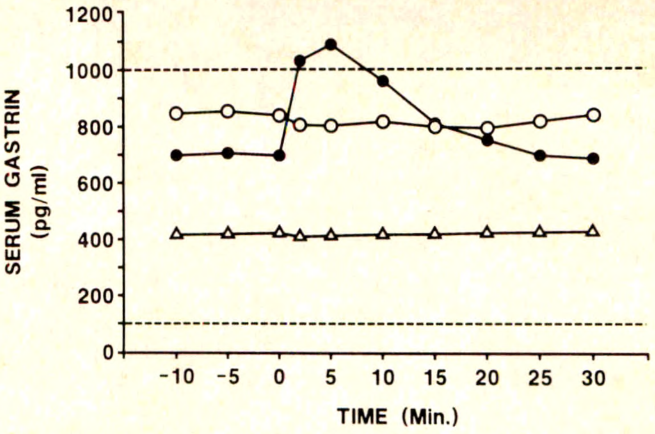


FIG. 2. Serum gastrin responses to intravenous secretin injection (2 U/kg) in patients with gastrinoma (closed circles), chronic atrophic gastritis and achlorhydria (open circles), or duodenal ulcer and gastric outlet obstruction (open triangles), with elevated but nondiagnostic fasting serum gastrin concentrations (100 to 1000 pg/mL). A positive test, consistent with the presence of gastrinoma, is indicated by an increase over basal serum gastrin levels of at least 200 pg/mL (from Wolfe and Jensen[21]).

TABLE 1. *Differential Diagnosis of Hypergastrinemia*

A. Hypergastrinemia Associated with Increased Gastric Acid
    1. Gastrinoma, sporadic or familial (MEN-I)
    2. Hypercalcemia
    3. Antral G-cell hyperfunction
    4. Antral G-cell hyperplasia
    5. Retained gastric antrum
    6. Short bowel syndrome
    7. Gastric-outlet obstruction
    8. Renal failure (acid secretion may be normal)

B. Hypergastrinemia Associated with Normal or Decreased Gastric Acid
    1. Pernicious anemia
    2. Chronic or atrophic gastritis
    3. Gastric ulcer (malignant or benign)
    4. Vagotomy
    5. Pheochromocytoma
    6. Therapy with H_2-receptor antagonists or Na^+-K^+-ATPase inhibitors

For those few patients with ZES in whom clinical suspicion is high but the standard secretin test is nondiagnostic (less than a two-fold or 200 pg/mL increase in gastrin), a combined secretin-calcium stimulation test has been shown to be superior and effective in the discrimination of these gastrinoma patients.[23] A one-minute infusion of 2 mg/kg of calcium gluconate, together with an intravenous bolus of 2 U/kg of secretin, has been shown to be effective in provoking a two-fold or 200 pg/mL increase in gastrin from ZES patients. Secretin infusion in normal subjects results in a transient depression of gastrin release from the normal G cells in the gastrin antrum. Conversely although nutrient ingestion, in the form of a test meal, readily stimulates a two-to-threefold increase in plasma gastrin in nongastrinoma patients, there is minimal increased gastrin secretion in response to a test meal in patients with ZES.[7,9,22,24] This lack of an apparent response to a test meal is believed to be secondary to a masking of the normal antral gastrin response to nutrients by the ambient high rates of secretion of gastrin from gastrinoma cells.

The gastrin responses to both a test meal and a secretin infusion test can be used to identify causes of hypergastrinemia other than Zollinger–Ellison Syndrome (Table 2). For example a rare cause of hypergastrinemia is antral G-cell hyperplasia, also known as pseudoZES, and results in high levels of plasma gastrin secreted from the antrum.[25] Patients with antral G-cell hyperplasia demonstrate a nonstimulatory response to secretin, but release high amounts of gastrin in response to a test meal, over and above their already-elevated basal values. These patients may have an aggressive ulcer diathesis related to their hypergastrinemia, which is curable by antrectomy.

Chemical analysis of the circulating forms of gastrin may also aid in the diagnosis of gastrinoma and in the identification of those patients with metastatic gastrinoma as opposed to nonmetastatic tumors. Gastrin may appear in the circulation in multiple forms, and a peptide precursor form of gastrin has been shown to be elevated in patients with gastrinoma.[26] Recent studies also suggest that measurements of serum gastrin levels using antibodies directed toward the amino-terminus and carboxy-terminus of the peptide may enable identification of metastatic tumors.[27] Chemical studies to elucidate the forms of gastrin present in the circulation may therefore prove useful in the evaluation of these patients; however further evaluation is required before such studies can be confirmed as clinically advisable.

Immediate Treatment and Metabolic Support

Therapy of Acid Hypersecretion

The immediate treatment of any patient with acid-peptic disease requires control of gastric acid secretion, and patients with suspected or proved ZES require meticulous antacid therapy. The introduction of Type 2 histamine (H_2)-receptor antagonists more than a decade ago made this goal a clinical reality, and with the newer generation of H_2-receptor blockers, gastric acid secretion can be abolished in virtually all patients. Relief of symptoms, however, does not necessarily reflect complete control of acid hypersecretion.[28] Therefore it is mandatory to confirm gastric neutralization with intragastric monitoring. A reduction in the amount of gastric acid secretion to less than 10 mEq/hour indicates adequate therapy,[7,21] and intragastric pH monitoring on a repeated basis is necessary to assure that a seemingly effective dose of medication remains so over several hours or days. Changes in a patient's metabolic status, inflammation and infection, hemodialysis, and other events may alter the effectiveness of antisecretory therapy, and pH monitoring should be maintained to ensure the continued adequacy of any therapy. Although all H_2-receptor blockers can be administered on an intermittent (q 6 hour) basis, it is more advisable to begin therapy with a continuous intravenous infusion, with subsequent titration of the dose based on intragastric monitoring. Patients with ZES require higher doses of H_2-receptor blockers than patients with common peptic ulcer disease, and may require up to 12 gm/day of cimetidine, up to 6 gm/day of ranitidine, or up to 1 gm/day of famotidine. In the acute setting, therapy of a patient with suspected ZES might consist of an intravenous infusion of 50 mg/hour of ranitidine or 10 mg/hour of famotidine as initial therapy.[21] Intragastric instillation of antacids may also help to control pain, although confirmation of neutralization of gastric acid secretion should be performed before administration of antacids. Continuous intravenous infusion of drug can be changed to intermittent oral therapy once acute symptoms have subsided and other complications, such as GI bleeding, have resolved. It is not unusual, however, for doses of H_2-receptor antagonists to have to be increased after therapy has been initiated,[28] and it is therefore imperative to confirm the effectiveness of antacid therapy after conversion to an intermittent dose schedule.

TABLE 2. *Serum Gastrin Response to Provocative Tests in Patients with Hypergastrinemia*

	Test		
Disorder	Secretin Injection	Calcium Infusion	Test Meal
Gastrinoma	Increase > 200 pg/mL (95 pM) over basal	Increase > 400 pg/mL (190 pM) over basal	NC or increase < 50% over basal
Hypochlorhydric states	NC, decrease, or increase < 200 pg/mL	NC or small increase	NC or increase < 50% over basal
Antral G-cell hyperfunction/hyperplasia	NC, decrease, or increase < 200 pg/mL	NC or small increase	Increase by >100% over basal
Other hyperchlorhydric states: Retained gastric antrum Short gut syndrome Gastric-outlet obstruction	NC, decrease, or increase < 200 pg/mL	NC or small increase	Increase by >50% over basal

* NC, no change.

Modified from Wolfe and Jensen.[21]

Nutritional Support

Patients presenting with acute complications of ulcer disease caused by gastrinomas frequently manifest nutritional deficiencies as well.[29] In addition to the effects of the acute ulceration and associated inflammation, patients may be malnourished due to malabsorption of nutrients secondary to acid-induced mucosal injury of the small intestine. Diarrhea and steatorrhea are present in up to 40% of gastrinoma patients, and objective evaluation of nutritional status frequently discloses evidence of malnutrition. A short-term weight loss of more than 10% of normal body weight, depressed plasma levels of albumin and total protein, and total lymphocyte counts less than 1000/mm^3 all suggest significant catabolism. Reversal of acid hypersecretion with resumption of normal nutrient intake is a major step in reversing malnutrition seen in ZES patients, and it has been demonstrated that therapy with H_2-receptor antagonists frequently results in a progressive weight gain for the first 10 to 14 days after initiation of therapy.[29] Aggressive nutritional support may be indicated, however, in the patient who is severely malnourished or whose ulcer complications prevent normal enteral feeding. Nitrogen losses, due to catabolism and shed blood, should be reversed promptly, and parenteral nutritional support is therefore frequently indicated for a period of 1 to 2 weeks. Plans for surgical intervention for tumor resection or definitive control of acid hypersecretion should therefore be delayed until these deficits in nutritional status have been reversed.

Tumor Localization

Diagnostic procedures in patients with suspected ZES should not rest with chemical confirmation of the presence of gastrinoma alone. The optimal management of the gastrinoma patient will also depend on the anatomic characteristics of the tumor(s), as well as the presence or absence of metastasis. Therefore it is essential that studies be undertaken to establish the extent and location of the neoplasm.

Noninvasive imaging studies such as sonography, computed tomographic (CT) scanning, and magnetic resonance imaging (MRI) may yield valuable information regarding the location of single or multiple adenomas, or the presence of metastatic disease. While generally free of side effects, these techniques have not been as efficacious as selective arteriography in detecting small tumors. Recently dynamic CT scanning (Fig. 3) was reported to have achieved sensitivity in the range of 75% to 80%,[30,31] which is comparable to the results achieved with combined transabdominal sonography, CT imaging, and selective arteriography in patients with ZES. Norton et al.[32] reported a 70% sensitivity rate for all studies combined, but also noted a 33% false-negative rate when none of the three studies disclosed presence of the tumor (Table 3). MRI is potentially of great value in the localization of even small islet-cell tumors,[33] and may be of particular use in the detection of metastatic gastrinoma (Fig. 4). New techniques of contrast enhancement to improve the ability of MRI to image small, completely intrapancreatic tumors, are currently in development.

When noninvasive studies indicate the presence of diffuse metastatic disease, invasive procedures are usually unnecessary for further definition of the tumor process. When no tumor is identified, however, or when imaging studies suggest the possibility of resectable lesions, further studies are indicated to precisely locate the gastrinoma and to aid in the operative strategy of attempted resection. Selective arteriography may reveal the tumor location in up to 80% of cases (Fig. 5) and is generally the most accurate preoperative localization technique.[32,34] Percutaneous transhepatic portal venous sampling studies may provide further evidence of the location of gastrinoma tissue,[35] and may be particularly useful when other localizing procedures fail (Fig. 6). The value of portal venous sampling studies in the setting of a positive tumor localization by other techniques is debatable, however. Furthermore the accuracy of venous sampling procedures greatly depends on the experience of the interventional radiologist. The most accurate localization procedure is the careful operative assessment of the splanchnic organs, aided by the use of intraoperative ultrasound.[36,37] The failure to locate gastrinoma tissue is usually related to the small size or multicentricity of tumors, and therefore any localization information that can be obtained from preoperative studies can be immensely valuable to the surgeon. Despite careful preoperative and operative efforts to identify the tumor, at least 20% to 30% of gastrinoma patients will have occult tumors, even in experienced hands.[11,14–16,32] Occult tumors, irresectable metastatic disease, or diffuse microadenomatosis are all commonly associated with MEN-I patients, and the confirmation of MEN-I Syndrome therefore generally precludes attempts at resection. In the absence of diffuse metastatic disease or familial forms of gastrinoma, all patients should, in general, undergo abdominal exploration in an effort to ascertain resectability of tumor. Contingency plans for the ultimate method of control of acid hypersecretion should be established before operation in case resection proves infeasible.

Treatment

Definitive management of the ZES patient includes treatment of the gastrinoma as well as treatment of acid hypersecretion. Whereas the approach to the disease was characterized until recently by surgical management of the acid peptic complications of the disease, with almost

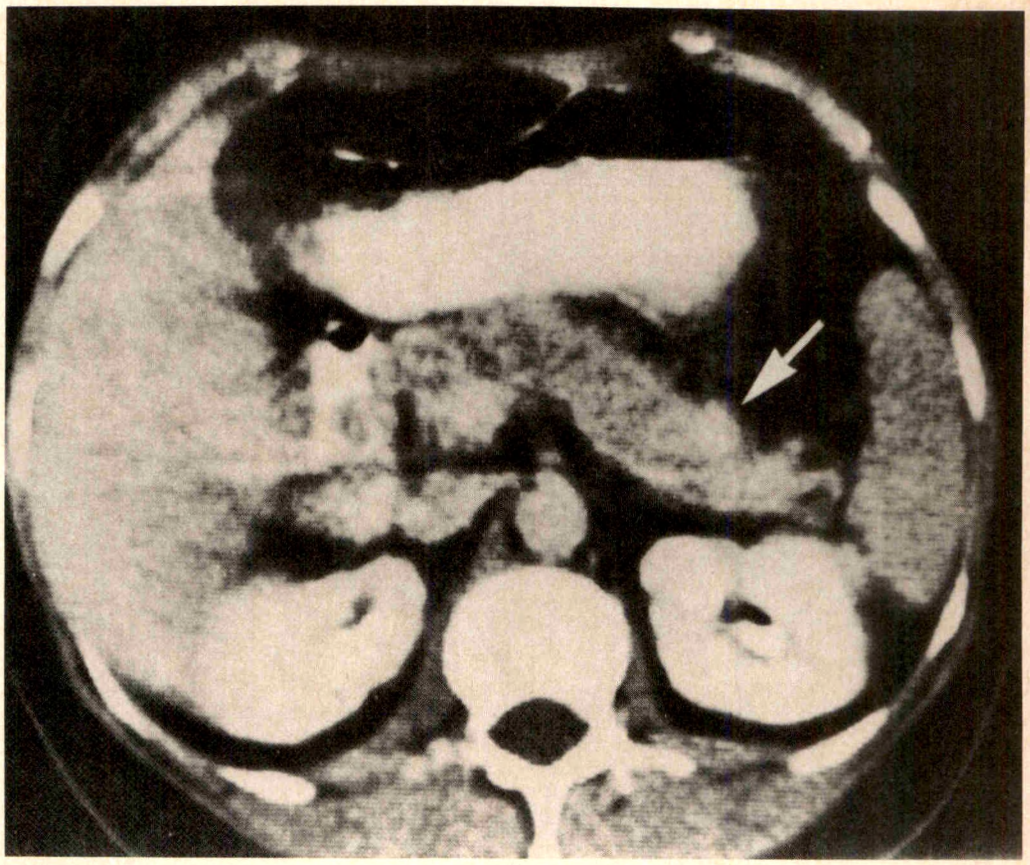


FIG. 3. Computed tomographic (CT) scan of patient with Zollinger–Ellison syndrome. CT scan with contrast injection reveals 1-cm enhancing lesion (arrow) within pancreatic tail that was confirmed at surgery as a gastrinoma (from Stark et al.[113]).

uniformly nonsurgical management of the tumor, *per se*, the roles of surgeons and gastroenterologists have now overlapped in both aspects of the disease. The uncertainty regarding responsibility for overall management has been contributed to by the development of more effective pharmacologic agents for the control of acid secretion, as well as the increasing emergence of data to support attempts at surgical cure of the underlying tumor. At this point, it cannot be assumed that either aspect of the management of the ZES patient will necessarily depend on surgical or pharmaceutical therapy. Each patient must be evaluated and treated individually, and an appropriate definitive care plan will depend on the specific anatomic presentation of the disease as well as the general medical, psychosocial, and geographic facts that apply.

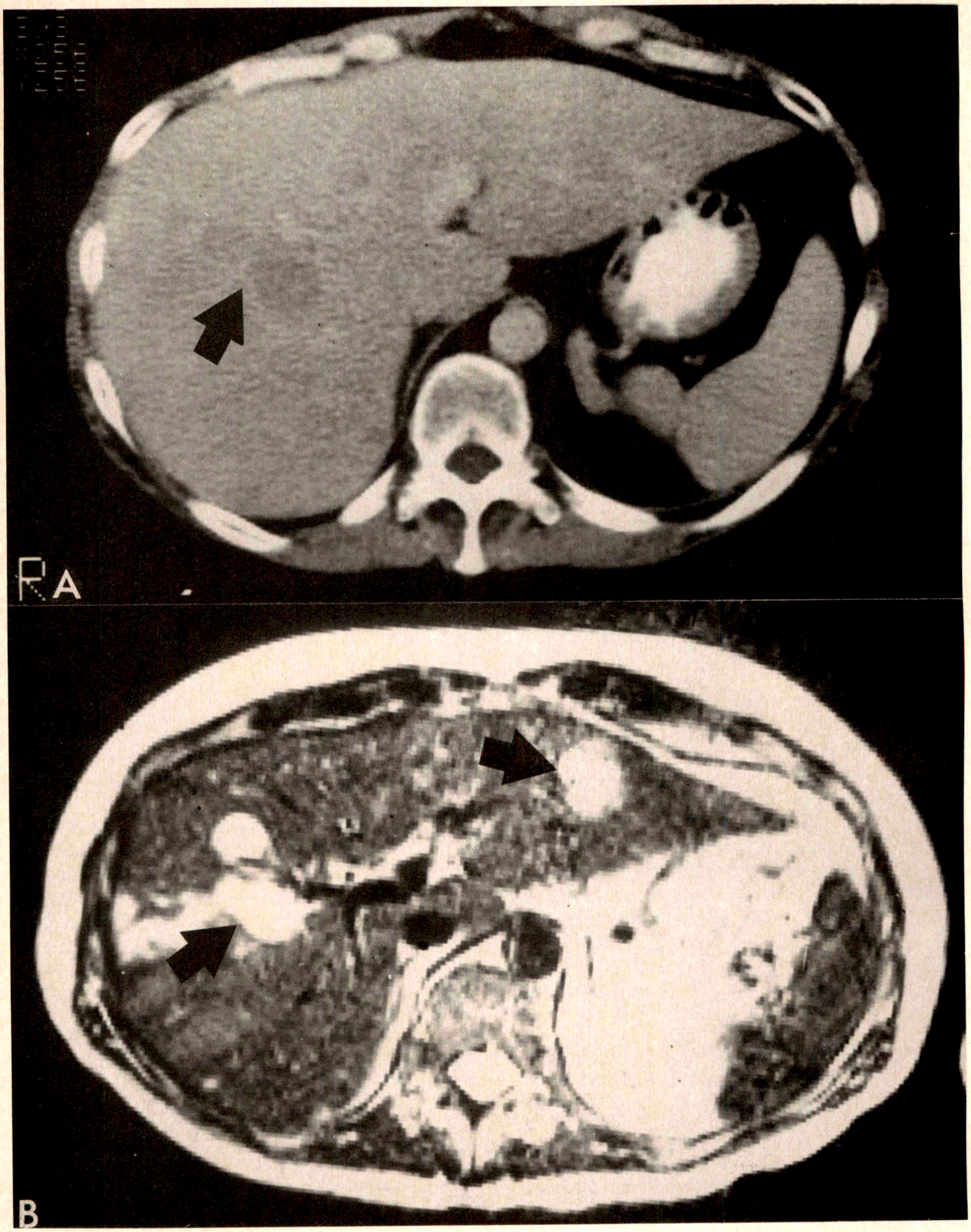
Treatment of Isolated Gastrinoma

The ideal therapy of any islet-cell tumor is resection for cure. The early experience with ZES indicated that curative resection was possible in only about 5% of cases.[14,17,38–40] Zollinger's own assessment of the results of the first 25 years' experience with ZES concluded that cure was rarely possible.[39] In this decade, however, several series have appeared that refute that approach, and rates of cure (defined as prolonged eugastrinemia and indepen-

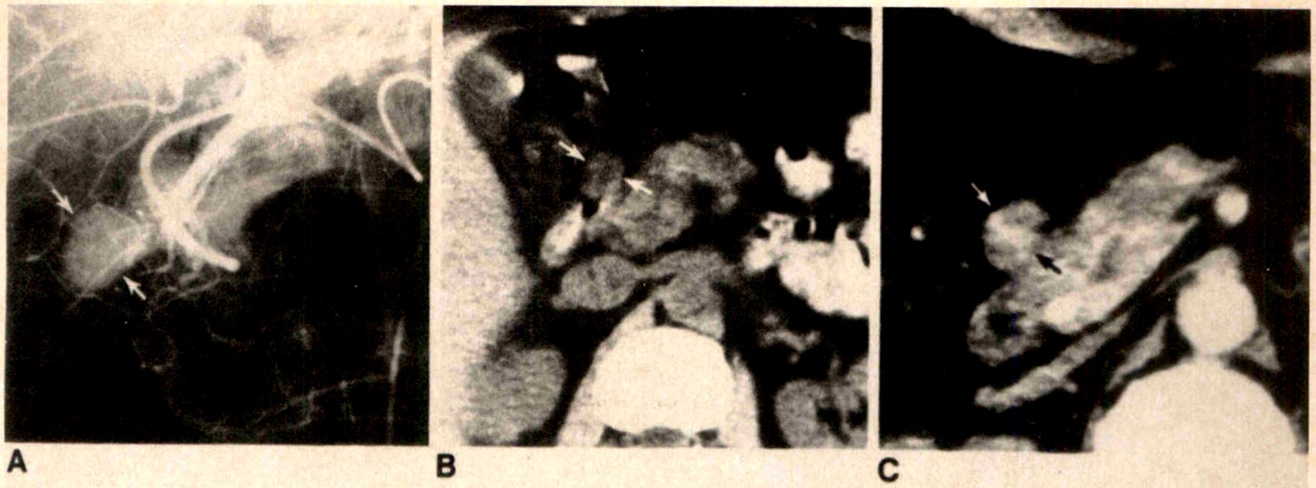
TABLE 3. *Accuracy of Imaging Techniques in Localization of Gastrinoma*

	Primary Gastrinoma		Metastatic Gastrinoma (Liver)		
Imaging Techniques	Sensitivity %	Specificity %	Sensitivity %	Specificity %	Reference Numbers
Ultrasonography	21–28	92–93	14	100	32, 112
CT scanning	35–59	83–100	35–72	98–100	30, 32, 112, 113
Selective angiography	35–68	84–94	33–86	96–100	32, 112, 114
Combined use of above techniques	70	92	—	—	32

Modified from Wolfe and Jensen.[21]



FIGS. 4A and B. Magnetic resonance imaging (MRI) of metastatic gastrinoma. Images obtained from patient with documented metastic gastrinoma are shown from CT scan (A) and T_2 image on MRI (B). Multiple intrahepatic metastases appear as enhanced areas on MRI. (Courtesy of David Gordon M.D., Department of Radiology, SUNY-HSC, Brooklyn, New York.)



FIGS. 5A–C. Comparison of selective arteriography with CT scanning in the localization of gastrinoma tumors. (A) Common hepatic arteriogram showing hypervascular gastrinoma (arrows). (B) Noncontrast CT scan showing gastrinoma as soft-tissue mass (arrows) anteriolateral to pancreatic head. (C) CT scan after intravenous contrast bolus showing tumor enhancement (arrows). At operation, gastrinoma found in peripancreatic lymph node. (From Krudy et al.[31]).

dence from antisecretory therapy after removal of all apparent tumor) now approach 30% to 40% in selected series.[11,12,32,41] As with any adenocarcinoma, recurrences after presumed curative resections have also been reported,[32,41–44] but in general, all patients with isolated gastrinoma, or in whom preoperative localization studies fail to demonstrate the location of the tumor, should undergo surgical exploration for assessment of localization and resection. Extrapancreatic tumors frequently elude localization studies, yet are the most curable (Table 4). It is an especially regrettable error, therefore, to conclude from the absence of radiologically demonstrable tumors that the patient is an unsuitable candidate for surgical exploration.

Small intrapancreatic tumors may be identified only with careful surgical exploration, combined with intraoperative sonography.[36,37] In a prospective series of the value of sonography in the operative identification of islet-cell tumors, both palpation and sonography were found to be equally effective in the identification of intrapancreatic tumors.[37] The sensitivity of intraoperative sonography was slightly higher (93%) than that for palpation alone (87%). In 11% of cases, the sonographic findings altered the management of the patient or served as the only successful method of tumor localization. An adenoma in the pancreatic head can frequently be identified by operative sonography and palpation, and when invasion of surrounding pancreatic tissue has been sonographically dismissed,[37] simple excision can be performed (Fig. 7). Intrapancreatic tumors are best managed by enucleation, or in the case of a lesion in the pancreatic tail, by distal resection (Fig. 8). Pancreaticoduodenectomy (Whipple procedure) has been associated with a substantial operative mortality rate when performed in ZES patients,[40,45] and should therefore be undertaken only when the likelihood of cure is high, and a lesser procedure is infeasible. In cases in which no tumor is detectable at operation, yet selective venous sampling studies have indicated a source in the pancreatic head, subsequent pathologic examination of the pancreas usually reveals multiple microscopic gastrinomas that would preclude cure by subtotal pancreatic resection.[17,45,46] Total pancreatectomy is to be avoided completely.

Extrapancreatic gastrinomas are most apparent on careful inspection and palpation. In their prospective series of laparotomies in ZES patients, Norton and colleagues[32] reported successful identification and removal of 24 tumors in 20 of 32 patients; locations included the pancreatic head (4), pancreatic body (1), pancreatic tail (3), peripancreatic lymph nodes (8), the pyloric channel (3), the duodenal wall (1), the jejunum at the ligament of Treitz (2), the ovary (1), and the liver (1). Tumors were therefore resected in 62.5% of operative patients; 6-month follow-up suggested biochemical cure in 30% of 28 patients who were free of hepatic metastases or MEN-I Syndrome at the time of surgery. These findings corroborated the earlier report by Malagelada et al.[12], that documented tumor resectability in 18 (41%) of 44 patients explored, with biochemical cure achieved in 20% of 35 patients without MEN-I Syndrome or hepatic metastases.

Long-term survival of gastrinoma patients correlates positively with successful tumor resection. Paradoxically patients who have no tumor demonstrable on preoperative or operative localization efforts also have a relatively favorable survival prognosis and may outlive patients with resectable tumors[41] (Fig. 9). ZES patients with surgically

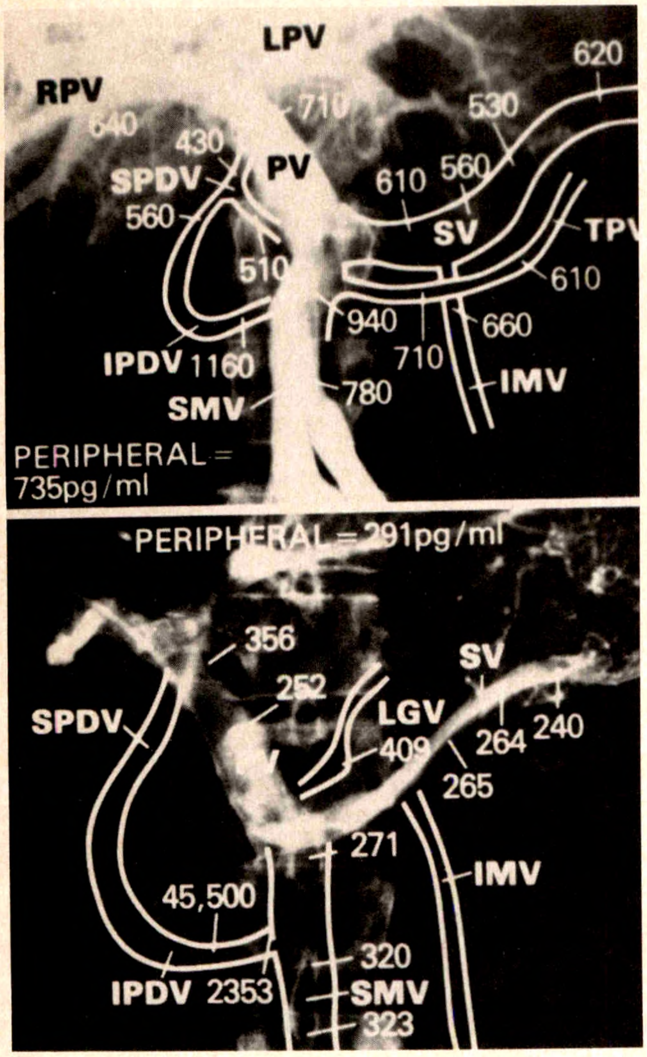


FIG. 6. Results of selective venous sampling for gastrin in two patients with Zollinger–Ellison syndrome. (Top) Numbers indicate gastrin concentrations (pg/mL) at each site shown. *Peripheral* refers to the simultaneous peripheral gastrin value. At operation a gastrinoma was found in lymph node adjacent to pancreatic head. (Bottom) Despite a large gastrin gradient arising from the inferior pancreatoduodenal vein, no gastrinoma was found at operation. PV = portal vein; RPV = right portal vein; LPV = left portal vein; SV = splenic vein; TPV = transverse pancreatic vein; IMV = inferior mesenteric vein; SMV = superior mesenteric vein; SPDV = superior pancreatoduodenal vein; IPDV = inferior pancreatoduodenal vein. (From Cherner et al.[124])

unidentifiable tumors may therefore represent an important subset of patients with the disease in which microscopic foci of adenomatosis, or G-cell hyperplasia, may be accompanied by little if any metastatic progression of disease. Because these forms of gastrinoma are frequently associated with the MEN-I Syndrome, the designation of MEN-I status has been regarded by some authors as a relative contraindication for resectability.[11,12,39–41] A patient with no apparent tumor or radiologic studies sugggestive of tumor who has documented MEN-I Syndrome is unlikely to have successful resection of an isolated gastrinoma. Conversely, however, the MEN-I patient with a single focus of tumor on preoperative studies should probably be regarded as a candidate for operative management of the tumor because successful control of progression of the disease has been observed in some patients.[37,38,47]

It is important to stress that in the non-MEN-I patient with a sporadic gastrinoma the final designation of no identifiable tumors implies that operative exploration has been carried out and has failed to reveal any gastrinoma tissue. It is not sufficient to conclude from negative radiologic studies alone that the patient does not have resectable isolated gastrinoma. With the exception of patients with obvious widespread metastases or MEN-I Syndrome, all patients should, in general, undergo exploration for attempts at surgical control of the gastrinoma.

Treatment of Diffuse or Metastatic Gastrinoma

Most gastrinomas are malignant and the presence of metastatic disease carries the lowest survival in patients with ZES. Gastrinomas are more indolent malignancies than other carcinomas of islet-cell origin, however, and the clinical patterns of metastatic disease vary greatly. Although hepatic metastases generally indicate the worst outcome, some patients have survived for more than 20 years with intrahepatic disease.[39,41,44,48] Therefore the presence of metastatic disease does not necessarily imply rapidly advancing disease, and overall 5-year survival rates reported for patients with disseminated malignancy ranges from 20% to more than 60%.[11,15,38,39,41,42,44,48,49]

A small minority of patients with seeming metastatic foci of gastrinomas have enjoyed prolonged periods of apparent cure after aggressive surgical therapy.[13] Isolated nodal metastases have been observed to respond favorably to resection, and a recent report documents a 75% to 85% 20-year survival in a small number of patients after resection of paraduodenal lymph node involvement with or without an identifiable primary gastrinoma.[50] It has been speculated that gastrinoma may arise *de novo* in lymphatic tissue,[13] although the presence of an occult primary tumor in these cases seems more likely. Careful examination of gastrointestinal tissue in patients undergoing aggressive regional resection for paraduodenal nodal involvement has revealed small intramural tumors ranging from the antrum to the proximal jejunum.[11,14,32,38,41,50] Prolonged eugastrinemia has also been documented in selected patients who have undergone resection of isolated hepatic metastases.[38,47] In one such case reported by Thompson and colleagues, death of the patient 4 years later due to unrelated causes allowed autopsy examination that disclosed an indolent pancreatic tumor.[51] In expert hands, therefore, patients with isolated metastatic deposits may still benefit from surgical resection.

TABLE 4. *Collected Rates of Cure After Resection of Gastrinomas*

Author	Year	Number of Patients	Length of Follow-up (yrs)	No. of Cures (%)	No. of Pancreatic Tumors	Duodenal Tumors	Extrapancreatic/ Extraintestinal
Rawson et al.[115]	1960	1	16	1	1		
Parrish et al.[116]	1965	1	6	1	1		
Zollinger et al.[117]	1968	25	20	1	1		
Zollinger et al.[39]	1980	15*	4–10	1		1	
Bonfils et al.[40]	1981	92	1–6	5 (5)		5	
Wilson[43]	1982	28	3–21	5 (18)	1		4
Friesen[11]	1982	23	3–10	10 (43)	6	2	2
Wolfe et al.[14]	1982	18	3–11	5 (28)		1	4
Barreras et al.[118]	1982	1	7	1	1		
Malagelada et al.[12]	1983	53	3–10	7 (13)	1	5	1
Deveney et al.[119]	1983	52	1–10	6 (12)	6		
Thompson et al.[110]	1983	27	1–4	3 (11)		1	2
Landor[120]	1984	1	2	1		1	
Stabile et al.[13]	1985	65	1.5–10	6 (9)	3	2	1
Miyata et al.[121]	1985	1	1	1			1
Norton et al.[47]	1986	52	0.5–4	7 (13)	2	1	4
Ellison et al.[41]	1987	20*	2–6	8 (40)	3	3	2
Total		475		69 (15)	26	22	21

Modified from Ellison et al.[41]

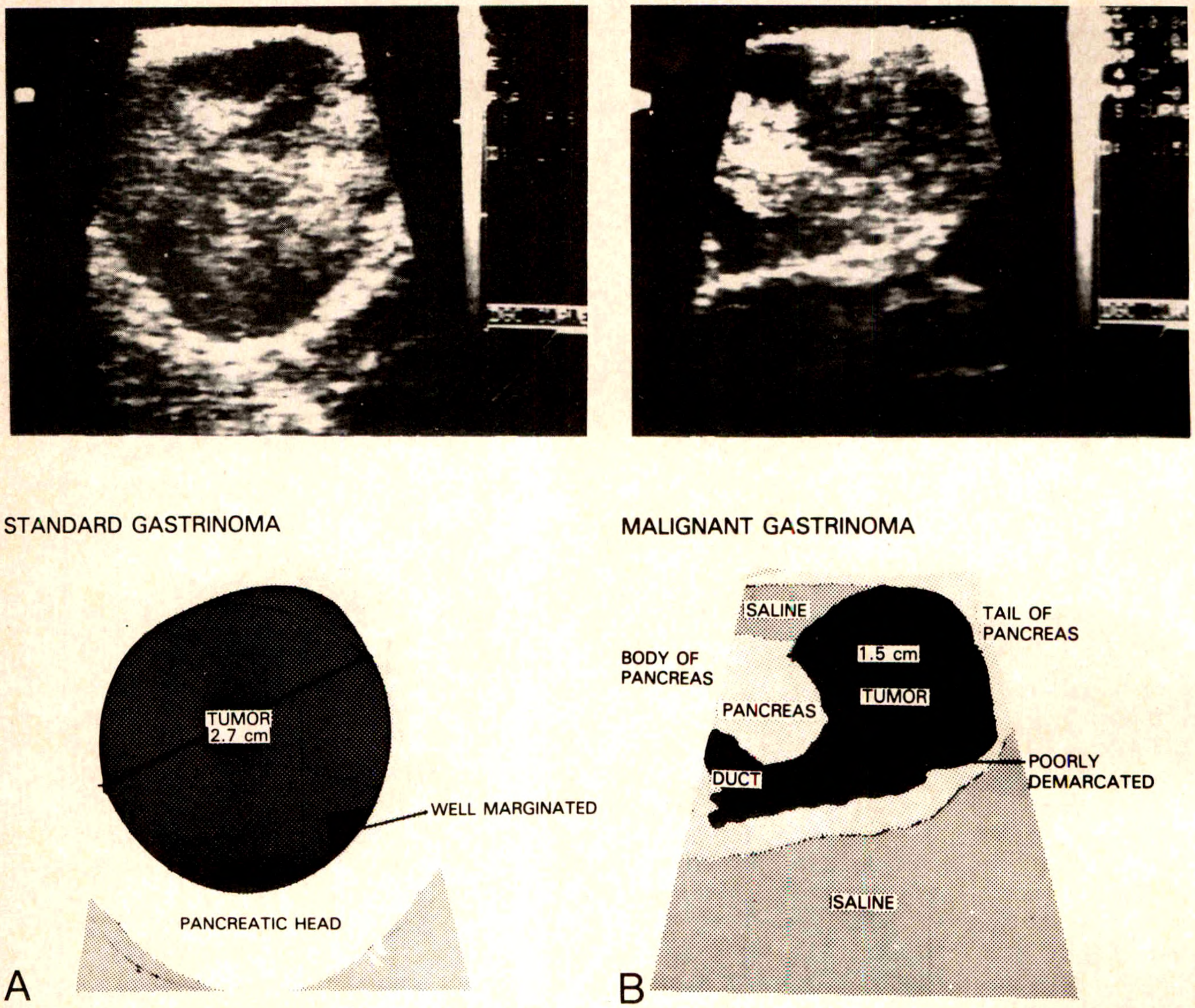
* Additional patients.

The majority of patients with metastatic gastrinoma are candidates for chemotherapy, and the pharmacologic treatment of the malignancy has undergone considerable evolution during the past decade as well. Since 1968, a first-line drug in the treatment of metastatic gastrinoma has been the islet-cell toxin streptozotocin.[52] While experience with this agent has varied in individual series of ZES patients, an overall response rate of 35% to 50% has been documented in patients with gastrinomas and other islet-cell carcinomas.[53,54] Patients frequently escape remission after a period of therapy, and gastrointestinal side effects and nephrotoxicity and hepatotoxicity have limited streptozotocin's usefulness.[55] Bone marrow suppression is unusual with this drug, however, and this fact has allowed trials of therapy with streptozotocin combined with 5-fluorouracil. This combination therapy resulted in a 63% response rate in a series of mixed islet-cell carcinomas, including gastrinomas, and was clearly superior to therapy with streptozotocin alone.[56] In an effort to avoid the substantial toxicity of these drugs, however, combination trials have been initiated with adriamicin, doxorubicin, and the newer agent chlorozotocin.[7,57–59] While initial experiences have been encouraging, further studies must determine the most efficacious form of chemotherapy of gastrinoma.

In addition to antimetabolic and cytotoxic agents, a new addition to the therapy of metastatic disease has been the use of analogues of somatostatin. This naturally occurring hormone is a potent inhibitor of both gastric acid secretion[60,61] and gastrin release.[60–63] Therapy with native somatostatin is limited, however, by a short circulating half-life of one to three minutes[64] and the resultant need for continuous intravenous infusion. Several potent and long-acting analogues of somatostatin have been synthesized recently,[65,66] and initial experience with one analogue, octreotide, has confirmed its potent inhibitory action on both acid secretion and serum gastrin levels in patients with ZES[67,68] (Fig. 10). A single subcutaneous injection of octreotide, also known as SMS 201–995, has a circulating half-life of approximately 120 minutes and suppresses serum gastrin levels in ZES patients for at least six hours.[68] This analogue has been found to be largely free of side effects and holds great promise in the treatment of gastrinoma. Studies are underway to determine whether treatment with octreotide should accompany initial therapy of metastatic disease.

Selective hepatic arterial embolization of metastatic gastrinomas has been attempted for the control of disseminated disease,[69] although the effect of angiologic therapy on survival is unknown. Native somatostatin has been documented to cause decreased splanchnic blood flow,[70,71] and tumor infarction has been observed in islet-cell carcinoma treated with octreotide.[67] Several observations of tumor regression after therapy with octreotide in patients with gastrinoma,[72] vipoma,[73] pituitary adenoma,[74] metastatic carcinoid,[75] and in experimental tumors,[76–78] raise the possibility of hormonal control of metastatic disease either through inhibition of nutrient supply to the tumor, or due to a direct antineoplastic effect. Further studies of this therapeutic approach are anxiously awaited.

Malignant islet-cell tumors are noteworthy for their capacity to secrete multiple peptide hormones, and this pleuripotential capacity has been well documented with



FIGS. 7A and B. Intraoperative sonography of intrapancreatic gastrinomas.(A) Typical appearance of benign islet-cell tumor, appearing sonolucent compared to surrounding pancreas, with a discrete margin and an echogenic rim around entire tumor. (B) Appearance of islet-cell tumor which had malignant features histologically. The border between the tumor and the surrounding pancreas is not clearly marginated, and the pancreatic duct was invaded by tumor. (From Norton et al.[37])

gastrinoma.[79,80] Metastatic gastrinomas have been reported to secrete insulin,[81] glucagon,[82] VIP,[82] and ACTH,[83] and may produce symptoms characteristic of excess states of these hormones. Similarly malignant insulinomas, glucagonomas, and vipomas may subsequently secrete excess levels of gastrin[82] and acquire the characteristics of ZES, including severe peptic ulcer disease. Therefore the long-term surveillance and management of metastatic gastrinoma should include special vigilance for the complications of other hormone-excess states, and changes in glucose tolerance and body habitus, or the development of diarrhea or hypertension, should be evaluated by appropriate endocrine testing.

The most common associated endocrinopathy in ZES patients is the MEN-I Syndrome, and hyperparathyroidism is noted in 5% to 20% of gastrinoma patients. The evaluation and therapy of the MEN-I gastrinoma patient requires special attention because ambient hypercalcemia may serve as a potentially reversible etiologic factor in some cases of ZES. In series of patients with documented MEN-I Syndrome and provocative studies diagnostic for ZES, parathyroidectomy and reversal of hypercalcemia have resulted in a restoration of normal gastrin levels.[84,85] In a series of ten patients, previously diagnostic gastrin responses to secretin challenge disappeared after parathyroidectomy in three patients, and patients appeared to be

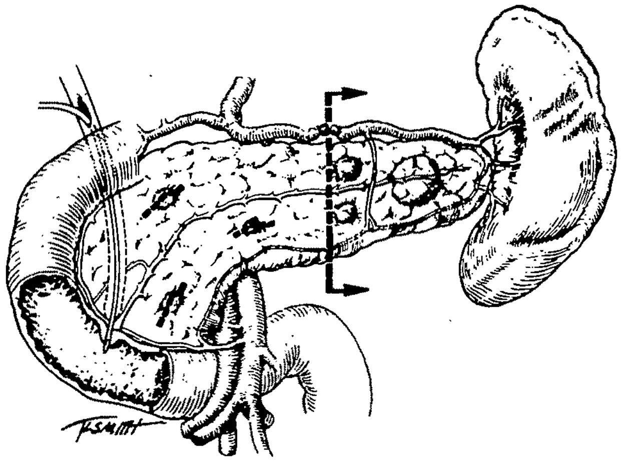


FIG. 8. Resection strategy for pancreatic gastrinoma. Gastrinomas that are multiple or present in distal gland are resected by distal pancreatectomy with *en bloc* splenectomy. Gastrinoma localized in proximal pancreas is excised by enucleation; incisions into the pancreatic parenchyma are made parallel to pancreatic duct to avoid ductular injury. External drains are placed near enucleation and resection sites. (From Zollinger.[125])

chemically cured of their gastrinoma status.[85] One possible explanation for these findings is the synthesis and secretion of gastrin by the hyperplastic parathyroid glands.[86] A more likely explanation is the unmasking of a secretin-responsive secretory mechanism in antral gastrin cells by high ambient levels of calcium.[84] Regardless of the mechanism, the clinical observation indicates that patients who present with chemical evidence of gastrinoma as well as hyperparathyroidism should undergo neck exploration first, with reassessment of gastrin status after correction of hypercalcemia. Patients who continue to manifest the chemical and clinical manifestations of ZES after parathyroidectomy may demonstrate improved sensitivity to antisecretory drugs[85] and may follow a relatively benign clinical course, despite the presence of metastatic disease.

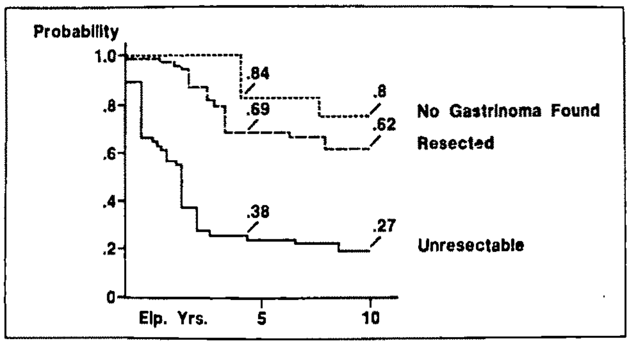


FIG. 9. Probability of survival in patients with and without surgical resection of gastrinoma. Survival of 55 patients operated on with no gastrinoma found (n = 7), gastrinoma resected (n = 10), and unresectable or metastatic gastrinoma (n = 38). Elp. Yrs. = elapsed years. (From Ellison et al.[41])

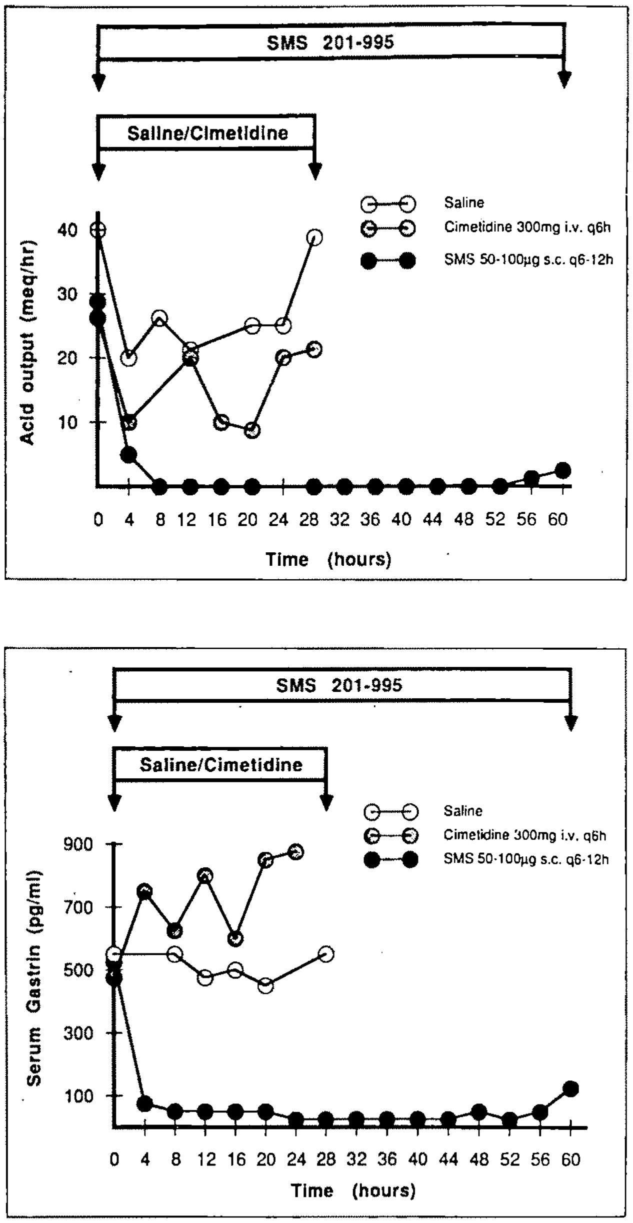


FIG. 10. Gastric acid and serum gastrin responses to saline, cimetidine, and somatostatin analogue (SMS 201-995) in three patients with benign gastrinoma. Nasogastric aspirates and serum samples were obtained during treatment intervals performed in random order in patients with documented gastrinoma after an overnight fast and withdrawal of prior antisecretory therapy. (From Vinik et al.[67])

Medical Treatment of Acid Hypersecretion

The therapy of excess gastric acid secretion underwent a revolution in the mid 1970s with the introduction of antagonists of Type 2 histamine (H_2)-receptors. Initial studies demonstrated that these agents were far more effective than anticholinergic therapy or direct intragastric buffering of acid with oral antacid preparations, and were generally effective in the treatment of ulcers in the majority of patients with peptic ulcer disease. Cimetidine,[29,87,88] and later ranitidine[89] and famotidine,[90] have been effective in the treatment of ZES patients as well, although treatment failure, drug side effects, and the requirement in some patients of extraordinary drug doses, have limited their success.

In collected series of more than 200 ZES patients treated with H_2-receptor antagonists (with or without anticholinergic agents), the average treatment failure rate was 20%[21] (Table 5). Therapy failure may manifest itself as symptoms ranging from persistence of dyspepsia to frank perforation or hemorrhage. Treatment failures are frequently ascribed to inadequate dosage of medication, inadequate follow-up quantitation of acid secretion, or failure of compliance to a medication regimen that frequently demands repeated dosing on a four-to-six-hour schedule. Problems with compliance may be related to quantity of pills ingested (up to 70 per day in some patients), cost of lifetime therapy (more than 20 years in most patients), or limited understanding of the disease process. Of particular concern, however, is the fact that the absence of symptoms does not necessarily imply the absence of mucosal disease.[28] Regular chemical, endoscopic, and gastric secretory evaluations are a mandatory component of medical therapy; increases in the required dose of medication are usually observed in virtually every patient treated with H_2-receptor antagonists.[91,92] Expected dose ranges that result in successful therapy of ZES patients range from 4 to 30 times the doses used in the treatment of routine peptic ulcer disease. As noted in a recent review by Wolfe and Jensen,[21] the median dose of medication required in ZES patients was 3.6 g/day for cimetidine,[93] 1.2 g/day for ranitidine,[92] and 0.25 g/day for famotidine.[90,94] As a result side effects of H_2-receptor therapy, such as gynecomastia and impotence, have been observed in up to 60% of male patients receiving cimetidine,[95,96] and drug-induced thrombocytopenia is a rare but worrisome development of ranitidine therapy.[97]

As a consequence of these concerns, attention has now turned to an entirely new class of antisecretory agents, the substituted benzimidazoles, of which omeprazole is the most extensively studied. These compounds inhibit the enzyme sodium-potassium ATPase, which serves as the final secretory step in parietal-cell hydrogen ion release (Fig. 11). Initial studies in patients with benign gastric and prepyloric ulcer disease demonstrated ulcer healing at 8 weeks in 96% of patients treated with 40 mg/day of omeprazole, and 89% of patients with 20 mg/day of omeprazole, compared to 85% of patients treated with 300 mg/day of ranitidine.[98] In ZES patients higher doses are required; the effective dose correlates directly with measured acid output, and averages more than 80 mg/day.[99] Because of a prolonged effect, however, patients can be treated with single-dose or twice-daily dose schedules, and all patients can be treated with 120 mg/day (six pills per day) or less. The absence of side effects during omeprazole therapy, the absence of chemical or hematologic toxicity, and the reduction in doses per day represents a major advantage in the treatment of ZES patients. As with H_2-receptor blocker therapy, patients must be monitored both chemically and endoscopically, and doses of medication must be adjusted as required at regular intervals. An increase in dose has been required in at least one fourth of the patients treated with omeprazole,[99,100] which still compares favorably with the need to increase medication in all patients treated with H_2-receptor antagonists. Interestingly a significant number of patients may require a decrease in omeprazole dose, and Maton et al.[100] report that 7 of 40 patients required reduction from an initial dose of 60 mg once a day as a consequence of the development of achlorhydria.

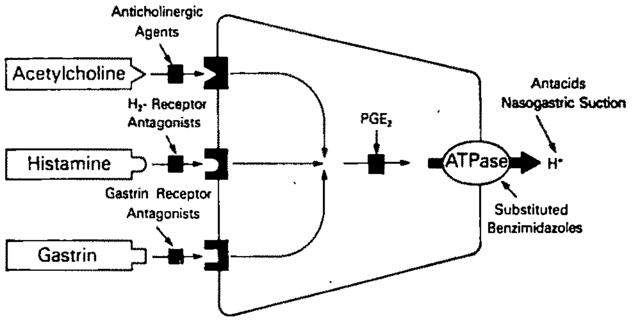


FIG. 11. Parietal cell schema illustrating pathways by which acid secretion is stimulated and the sites of action of various therapeutic agents. PGE_2 = site of inhibition by prostaglandin E_2 derivatives. ATPase = Na^+-K^+-ATPase, which is inhibited by substituted benzimidazoles. (From Jensen et al.[7])

While therapy with omeprazole or H_2-receptor antagonists does not alter the high circulating levels of gastrin in ZES patients, prolonged treatment with omeprazole in normal subjects is associated with hypergastrinemia, presumably on the basis of induced achlorhydria.[101] Achlorhydria is associated with elevated antral gastrinemia,[102] which in turn is associated with the development of enterochromaffinlike (ECL) cell (gastric carcinoid) tumors.[103,104] Initial studies with omeprazole in animals demonstrated the development of gastric carcinoids in a large percentage of rats, but not mice, when administered over a period of 2 years,[105] and ECL-cell proliferation appears to result from hypergastrinemia during omeprazole treatment in this animal model.[106] In the report by Maton et al.,[100] twelve patients had received omeprazole for more than 3 years, and serial gastric mucosal biopsies in all patients showed no evidence of carcinoid formation. When gastric acid analysis revealed absolute achlorhydria, however, the dose of omeprazole was reduced to avoid this potential complication. Basal gastric acid output therefore should probably be maintained above 0 mEq/hour, but below 10 mEq/hour, in patients receiving omeprazole.

Although the general availability of omeprazole awaits further confirmation of its safety, it appears likely that inhibitors of sodium-potassium ATPase may take their place as the preferred method of medical therapy of ZES. The addition of a somatostatin analogue may obviate the concern regarding the long-term consequences of hypergastrinemia, and trials of combination therapy with these agents are underway. Recent advances in the pharmacologic therapy of gastrinoma indicate the high likelihood of successful long-term management with these agents, although scrupulous patient compliance and meticulous attention to chemical and endoscopic status of the patient are clearly required for successful therapy.

Surgical Treatment of Acid Hypersecretion

Since Zollinger and Ellison's initial report of fulminant peptic ulceration in association with gastrinomas,[1] total gastrectomy has served as an extremely reliable means of controlling the peptic ulcer diathesis.[11,20,39,40,42,43,107–110] Multiple trials with H_2-receptor antagonists and omeprazole in the treatment of ZES have shown that the control of peptic ulceration achieved with medication alone approaches the results seen after total gastrectomy,[87–90,99,100] and both approaches are effective in the majority of patients treated. The use of total gastrectomy in the management of ZES rests on the definitiveness of the procedure in halting acid production, the removal of patient compliance as a variable in a lifetime of antisecretory therapy, and the generally benign postoperative response to total gastrectomy seen in ZES patients compared to that observed after total gastrectomy for other indications. If the insidious cause of ZES cannot be altered by removal of the tumor, then the proved efficacy of total gastrectomy must be weighed against the requirement for a lifetime of strict adherence to a pharmacologic regimen. The choice of medical therapy commits the patient to regular gastric acid and endoscopic evaluations, regardless of the absence of symptoms, to ensure appropriate drug dose and meticulous compliance. For patients deemed unreliable or unwilling, or for whom close follow-up is unlikely, this course may be unsuitable.

Failure rates for H_2-receptor blockade average 20% and may be less than 5% for omeprazole (Table 5). The reported failure rate of therapy does not always indicate the true incidence of inadequacy of medical therapy, however. In a series of 40 ZES patients selected to undergo a trial of omeprazole at the National Institutes of Health,[100] all patients had been previously treated with H_2-receptor antagonists, with or without anticholinergics, and all patients

TABLE 5. *Collected Rates of Treatment Failure with Long-Term Medical Therapy of Acid Hypersecretion in Zollinger–Ellison Syndrome*

Therapy	Patients (n)	Duration of Treatment (mo)	Failure n (%)	Reference no.
H_2-Receptor Antagonists				
Cimetidine	13	—	8 (61)	92
	14	11	0 (0)	29
	17	26	11 (65)	88
Cimetidine plus anticholinergic agent(s)	61	12	5 (8)	87
	20	33	10 (50)	109
	18	29	1 (6)	12
Ranitidine	15	18	6 (40)	89
Ranitidine plus antichol. agent	19	14	0 (0)	93
Famotidine plus antichol. agent	32	10	0 (0)	90, 94
Total	209		41 (20)	
Na^+-K^+-ATPase Inhibitor				
Omeprazole	7	14	0 (0)	99
	40	20	3 (8)*	100
	7	15	1 (2)†	122
	80	19	6 (8)†	123
Total	134		10 (7)	

* Acid secretion controlled to <10 mEg/hr in all pts. 3 pts reported no improvement in Sx; one pt developed a mucosal lesion.

† Acid secretion controlled to <10 mEg/m before total gastrectomy performed.

Modified from Wolfe and Jensen (21).

met criteria for successful therapy, *i.e.*, basal acid output was less than 10 mEg/hour. On close inspection, however, 29 of the 40 patients described symptoms of hyperacidity including epigastric pain (13), heartburn (11), diarrhea (8), anorexia (6), nausea (4), dysphasia (3), and vomiting (2). In addition, 17 of the 40 patients demonstrated a mucosal abnormality on endoscopic evaluation, including esophageal stricture formation (3), gastritis (3), duodenitis (5), and stomal ulceration or inflammation after partial gastrectomy (3). Success with medical therapy, even for the NIH group, is, therefore, a relative term.

No matter what the reason for failure of medical therapy, it must be recognized that an unfavorable response can result in the need for emergent surgical management of a peptic ulcer complication, with its attendant risk of morbidity and death. Even with the advent of more effective inhibitors of gastric acid secretion, the selected use of total gastrectomy in specific patients is an important component of the management of gastrinoma.

Total gastrectomy could not be justified in the treatment of as indolent a condition as gastrinoma if the elective operative mortality rate were high. Death after total gastrectomy in 137 patients in the gastrinoma tumor registry before 1974 was 11%.[49] More recent reports indicate that with modern technique, and preoperative control of acid hypersecretion, postoperative mortality for total gastrectomy in ZES patients ranges from 0% to 5% in reported series (Table 6). Unfavorable results generally occur only in patients operated on emergently, or in those with previous gastric surgery.[20,39,40,110] Weight loss and nutritional deficiency are well described complications that occur in the long term after complete gastric resection; the postoperative nutritional status in ZES patients who have undergone total gastrectomy has been documented to be generally satisfactory,[110] however. Intestinal adaptation to total gastrectomy may be enhanced by the trophic effects of hypergastrinemia in light of the fact that ZES patients generally tolerate gastrectomy with fewer nutritional complications than other patients subjected to the same procedure.[108,110] Postoperative symptoms may include the dumping syndrome, diarrhea, or complications (stenosis or reflux) of the esophagojejunal anastomosis.[12] Serious postoperative symptoms related to these complications are seen in fewer than 20% of patients, however.[11,12,39,40,42,43,45,107–110]

TABLE 6. *Modern Series (1978–1983) of Total Gastrectomy in Patients with Zollinger–Ellison Syndrome (Operative Mortality)*

Author (Ref. no.)	No. of Patients	No. of Deaths
Bonfils et al.[40]	57	8*
Brennan et al.[107]	6	1
Deveney et al.[42]	38	1
Friesen[11]	16	0
Jones[108]	14	0
Modlin et al.[20]	9	1†
Stabile et al.[109]	10	0
Thompson et al.[110]	23	0
Wilson[43]	16	0
Zollinger et al.[39]	34	1†
Total	223	12

Overall operative mortality rate: 5.4%

Operative mortality rate excluding emergency gastrectomy: 2.8%

Modified from Thompson et al.[110]

* Includes four with total gastrectomy done as an emergency; four with previous gastric surgery.

† Total gastrectomy done as an emergency.

The use of H_2-receptor antagonists combined with vagotomy has recently been proposed to offer an advantage over medical treatment alone by reducing the requirement for medication, and Richardson et al.[111] have advocated the use of proximal gastric vagotomy as an alternative to total gastrectomy when tumor resection is judged impossible at laparotomy. While a significant reduction in medication requirements secondary to the performance of the vagotomy seems to be an attractive alternative to high-dose medical therapy alone, the requirement for long-term medical compliance remains, and evidence that vagotomy results in a permanent or long-term reduction in medication dosage remains unknown. For the patient with minimal acid hypersecretion and no demonstrable tumor at operation, a lesser procedure, such as parietal cell vagotomy, may facilitate long-term therapy of what will probably be a relatively benign and prolonged course of therapy. For patients with vigorous acid secretion or disseminated metastatic disease, definitive control of acid secretion can only be assured with total gastrectomy.

In MEN-I patients with accompanying hypercalcemia, the surgical control of acid hypersecretion should begin with neck exploration for parathyroidectomy. Reassessment of basal and stimulated gastrin levels should be made after correction of hypercalcemia because gastrinoma status, and therefore the need for further antisecretory therapy, may be reversed in a minority of these patients.

Successful treatment of acid hypersecretion can be achieved with either surgical or pharmacologic therapy in ZES patients. The low mortality risk reported for total gastrectomy must be weighed against the generally unreported mortality risk of the failure of medical therapy. A minority of patients will demonstrate symptoms or complications after gastrectomy, as will a minority of patients who are treated with medical therapy alone. The management of acid hypersecretion must be individualized, and factors that indicate operative or nonoperative treatment include the extent and virulence of the disease, the age, nutritional status, and compliance of the patient, the ability or desirability to adhere to a regimen of follow-up chemical and endoscopic studies, the coexistence of additional disease states that may complicate drug or surgical therapy, as well as psychosocial and geographic factors. Long-term success in the treatment of this disorder therefore requires the judicious choice of treatment options, as well as aggressive and meticulous attention to the patient.

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Time Trends in Peptic Ulcer Surgery, 1956 to 1986

A Nation-Wide Survey in Sweden

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To establish time trends in surgical rates for peptic ulcer disease, all surgical departments in Sweden were requested to complete a questionnaire regarding elective operations for gastric and duodenal ulcers and emergency operations for ulcer perforations performed in 1956, 1966, 1976, and 1986. A total of 8558 operations were reported for these years. The incidence of elective surgery declined steadily, the rates being 72.1, 45.0, 31.9, and 10.7 per 100,000 inhabitants. The male:female ratio fell from 4.2 to 1.5:1, while the duodenal/gastric ulcer ratio remained virtually unchanged. The operation rate for perforation decreased by 50%, from 12.8 to 6.4 per 100,000 inhabitants. We conclude that there has been a dramatic decline in elective peptic ulcer surgery in Sweden that began long before the advent of fiberoptic endoscopy, highly selective vagotomy, or H_2-receptor antagonists. The comparable decline in emergency procedures suggests that true changes in the incidence or severity of the disease have occurred. In the future the few patients still needing elective surgery for peptic ulcer may have to be served by a small number of specialized centers.

THERE HAS BEEN a marked change in the epidemiology of peptic ulcer disease during the past century. In the 1800s duodenal ulcer was rarely encountered, but it became several times more common than gastric ulcer during the first half of the 20th century.[1] In the 1950s, however, the rise in duodenal ulcer incidence leveled off and there are now even strong indications that the disease is becoming less common.[2] According to mortality statistics and hospital admission rates, the decline in peptic ulcer is especially marked for duodenal ulcer in men.[2] The decrease in admittance rates is also accompanied by decreasing surgical rates.[3-5] As demonstrated in Rochester, Minnesota, there was a marked decline in elective operations for peptic ulcer during the last three decades, whereas the rates for emergency operations remained virtually unchanged.[3] The aim of this study was to assess trends in peptic ulcer surgery across the entire population of Sweden for the past 30 years.

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Materials and Methods

Swedish Health Care System

The Swedish health care system is almost entirely public, organized and run within each of 24 counties by the County Council. In each county there is at least one county hospital, with catchment areas ranging from 80,000 to 140,000 inhabitants. There are also 57 local county hospitals, serving 30,000 to 80,000 inhabitants each, while 12 referral hospitals serve both the immediate vicinity as the county hospital and a larger area as a referral center. Each individual is obliged to resort to one of the hospitals in the county for in-patient care unless sent to the referral center by a senior specialist in the local hospital. However, few patients are referred for peptic ulcer disease. There are also two small private hospitals in Sweden, which were excluded from the study because the number of peptic ulcer operations performed is negligable.

Questionnaire

We asked all surgical departments in Sweden for information on the number and sex distribution of elective and emergency operations for gastric and duodenal ulcers performed in 1956, 1966, 1976, and 1986, respectively. The number of reoperations was also requested. Exact figures, not only estimations, from the local registries were required for acceptance into the analysis. Each hospital keeps records of the number of patients cared for as well as operation codes and diagnoses according to the International Classification of Disease coding system. Of course

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Preliminary data from this material have been reported at Lars Thorén Day in Uppsala in December 1987, at the Nordic Ulcer Day in Gothenburg in January 1988, and at Digestive Disease Week in New Orleans in May 1988.

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the efficacy of the indexing might vary from hospital to hospital.

Departments responding promptly after the first letter were classified as early responders. Those responding after one or two reminders were classified as intermediate responders. The remaining departments were contacted and requested to complete a simplified version of the questionnaire. Complying centers were classified as slow responders. To identify potential biases, each category of responders was analysed separately.

Partial responses, *i.e.*, unanswered questions or answers containing estimations in an otherwise completed questionnaire, were dealt with as missing values in the calculations, while the rest of the information given in such a questionnaire was included. Therefore, the number of hospitals contributing to an average might vary.

Parallel with the collection of surgical data, all hospital administrations were requested to give exact catchment areas of their hospitals in 1956, 1966, 1976, and 1986 so we could calculate the population base covered by each hospital.

Results

Compliance

Of a total of 93 departments of surgery in Sweden, 20 were early responders and 56 were intermediate responders. Of the remaining 17 departments, 5 were slow and 12 were nonresponding hospitals (8 local and 4 county hospitals) (Fig. 1, Table 1). Thus the nonresponse rate was 13%. Five responding hospitals were small local ones and they informed us that ulcer patients (both elective and emergency cases) from their area had surgery at other hospitals in the county. Three additional local hospitals did elective procedures for ulcers but did not have any emergency service and thus sent their patients requiring acute operations to other hospitals.

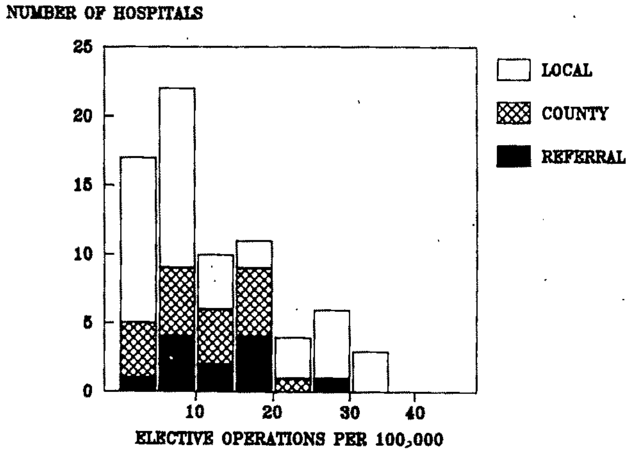

FIG. 1. Number of elective peptic ulcer operations per 100,000 inhabitants performed in Swedish hospitals by type of hospital (referral, county, local county) during 1986. A skewed distribution was found with one half of the hospitals performing less than ten operations per 100,000 inhabitants per year.

TABLE 1. *Response Status by Type of Hospital**

	Early	Intermediate	Slow	Nonresponsive	Total
Referral	1	11	0	0	12
County	8	12	0	4	24
Local county	11	33	5	8	57
Total	20	56	5	12	93

* The nonresponse rate was 13%.

Of the 81 responding hospitals, 12 could not be included in the analysis of secular trends because they had either begun operation during the 30-year period or stopped doing this type of surgery. Furthermore, in the large cities served by more than one hospital, the exact catchment area had varied, which made the calculation of proper population-based surgical rates for 16 hospitals virtually impossible. Moreover data from one or more of the selected years (1956, 1966, and 1976) were missing for 14 hospitals. Thus there remained 39 hospitals covering a stable population of 3.2 to 3.4 million inhabitants from which we obtained complete information—current and historic—with respect to surgical activity as well as to demography of their catchment areas. Of course surgical rates for 1986 calculated from this smaller data base differs slightly from the calculations based on the entire population (Tables 2–4).

Number of Operations in 1986

In 1986, a total number of 860 elective operations for peptic ulcer were performed in a population of 7 million people (Table 2), thus giving a rate of elective operations of 12.2 operations per 100,000 inhabitants. The elective

TABLE 2. *Number of Elective Operations and Emergency Operations for Perforation for Peptic Ulcer Disease in Sweden, 1986*

Type of Operation	Outcome	Reporting Hospitals
Elective Operations		
Number	860	76
Operations/100,000*	12.2	76
Male/female (ratio)	410/316 (1.3:1)	55
DU/GU (ratio)	394/380 (1.0:1)	59
DU: male/female (ratio)	212/127 (1.7:1)	42
GU: male/female (ratio)	171/177 (1.0:1)	49
Operations for Perforation		
Number	434	73
Op for perforation/100,000†	6.5	73

* Catchment population is 7,060,000.
† Catchment population is 6,970,000.
DU, duodenal ulcer; GU, gastric ulcer.

TABLE 3. *Elective Surgical Procedures for Peptic Ulcer Disease in 39 Swedish Hospitals for 4 Selected Years*

Variable	1956	1966	1976	1986
Number	2299	1455	1077	366
Population (×1000)	3188	3232	3373	3427
Op/100,000	72.1	45.0	31.9	10.7
Male/female	605/145	653/176	503/218	174/119
Male/female ratio	4.2:1.0	3.7:1.0	2.3:1.0	1.5:1.0
DU/GU	1005/688	709/571	542/453	182/150
DU/GU ratio	1.5:1.0	1.2:1.0	1.2:1.0	1.2:1.0
DU: Male/female	350/64	369/87	223/65	101/51
DU: Male/female ratio	5.5:1.0	4.2:1.0	3.4:1.0	2.0:1.0
GU: Male/female	206/72	262/98	215/103	60/67
GU: Male/female ratio	2.9:1.0	2.7:1.0	2.1:1.0	0.9:1.0

DU, duodenal ulcer; GU, gastric ulcer.

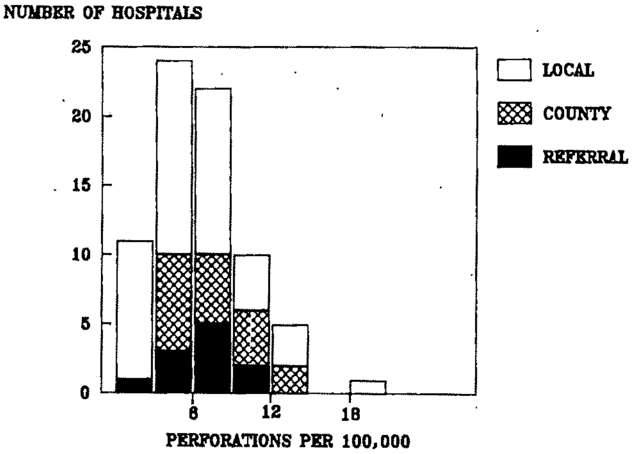

FIG. 2. Number of emergency operations for perforation per 100,000 inhabitants performed in Swedish hospitals by type of hospital (referral, county, local county) during 1986. The distribution is bell-shaped, indicating that deviations from a national mean occur more at random in comparison with the elective surgical rate.

surgical rate varied tenfold between hospitals (Fig. 1) without any distinct pattern with regard to geographical location, size, or type of hospital. Just over one half of the hospitals did less than ten operations per 100,000 inhabitants, while only four did more than 30 per 100,000. Rates for individual hospitals varied from 0 to 38 operations per 100,000 inhabitants. The mean rates for elective operations were 13.5%, 8.5%, and 10.0% in referral, county, and local county hospitals, respectively (Student's t test; $p > 0.05$).

The number of operations performed for perforation in a population of 6.6 million people in 1986 was 434, and the rate was 6.5% per 100,000 inhabitants (Table 2). Rates for individual hospitals varied from 0 to 18 operations per 100,000 inhabitants (Fig. 2). The mean rates for emergency operations for perforation were 5.7%, 5.6%, and 4.8% in referral, county, and local county hospitals, respectively (Student's t test; $p > 0.05$).

A linear regression analysis between the number of elective procedures and emergency operations for perforation revealed that there was no statistically significant correlation whatsoever, the correlation coefficient being −0.07 (Fig 3). The absence of a positive correlation between rates for elective procedures and perforations indicates that the high elective rates observed in some hospitals cannot be explained by higher incidence rates of peptic ulcer disease in their catchment areas. If such high-incidence areas existed, one would expect that a large number of elective procedures would be coupled to a large number of perforations, thus giving a positive correlation. Absence of a negative correlation indicates that an active elective surgical policy does not result in any noticable protective effect on a populational level, at least as far as perforations are concerned. It is highly unlikely that both mechanisms in operation simultaneously balance or negate each other completely.

Secular Trends in Surgical Rate

Exact figures for the number of elective and emergency operations during all of the 4 years under study (1956, 1966, 1976, and 1986) were obtained from 39 hospitals

TABLE 4. *Number of Emergency Operations for Perforation in 33 Swedish Hospitals for 4 Selected Years*

Variable	1956	1966	1976	1986
Number	334	225	237	179
Population (×1000)	2608	2628	2748	2801
Op/100,000	12.8	8.6	8.6	6.4

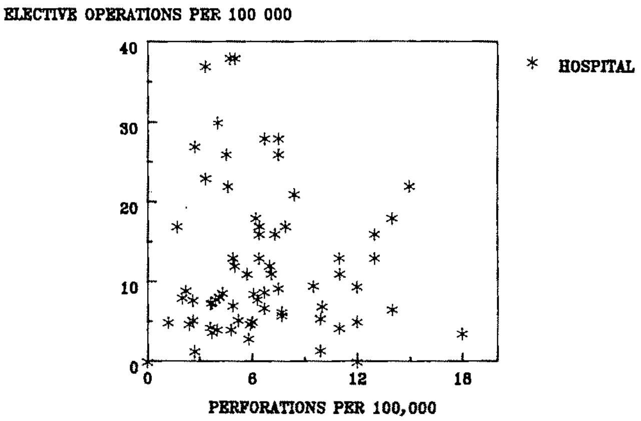

FIG. 3. Correlation between elective surgical rate and emergency operation rate for perforation. A lack of positive correlation indicates that there are no high incidence areas for peptic ulcer disease in Sweden. A lack of negative correlation indicates that more elective surgical activities does not protect the population against ulcer complications.

representing a population gradually increasing from 3.2 to 3.4 million during the 30-year period. In this population, the rate of elective procedures decreased steadily, from 72.1 to 10.7 per 100,000 people (Table 3; Fig. 4). The ratio between duodenal and gastric ulcers remained essentially unchanged, and thus the decline was equally pronounced for both ulcer sites. However the male predominance became less marked during the study interval. In 1956 four of five elective operations were performed in men, while operations in men were only 50% more common than in women in 1986.

The operation rate for perforation fell from 12.8 per 100,000 inhabitants in 1956 to 6.4 per 100,000 people in 1986 (Table 4; Fig. 4). Thus the number of operations for perforation decreased by 50% during the 30-year period.

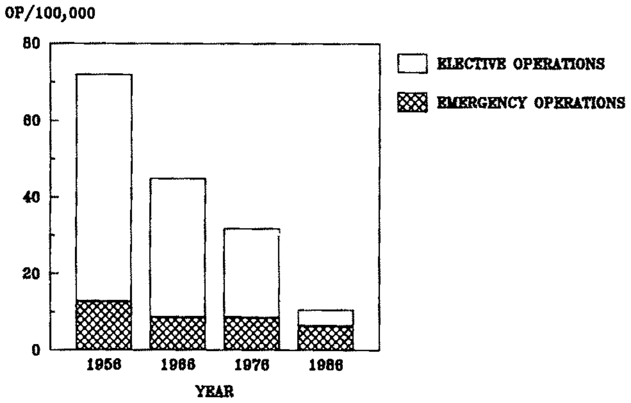

FIG. 4. Rates for elective operations and emergency operations for perforations during 4 selected years.

Control Analyses

The surgical rates for elective operations and for emergency operations for perforation did not differ significantly between early, intermediate, and slow responders (Figs. 1 and 2). There were no statistically significant differences with respect to the distribution of referral, county, or local county hospitals, and the response categories did not differ with respect to trends over time. Also hospitals giving full historic data had about the same elective surgical rates as those that did not.

Discussion

The main finding in this study was a steep decline (−85%) in elective ulcer surgery in Sweden during the past 30 years. The downward trend was not confined to any particular ulcer site and the fall was almost equally pronounced for gastric ulcer as for duodenal ulcer. On the other hand, it seems as if the rates for male and female patients were somewhat differently affected, with a steadily falling male:female ratio. There was also an unequivocal decline in operations for perforated peptic ulcer, and the reduction of operation rate was approximately 50%.

Before drawing any conclusions from the present data, some comments regarding the validity must be made. The information was obtained by sending questionnaires to the heads of every surgical department in Sweden. They were asked to extract the requested data from their own registries. There is of course a risk of negligence, but our impression is that the questionnaires have been completed with great care. Moreover only exact figures were accepted in the analysis. The results obtained suggest that registries over surgical operations are, in general, well managed, making misclassification as a major source of error highly unlikely. The unchanged ratio between gastric and duodenal ulcers also makes this explanation less plausible. A nonresponse rate of 13% may be a matter of concern; but by analyzing type, size, and geographic location of nonresponding hospitals, we found no specific differences in comparison with responding ones.

Partial nonresponse, *i.e.*, missing historic data, may also have introduced bias. However no systematic difference emerged when we compared the figures from 1986 derived from those departments that presented a complete record for the 4 years under study, with those from departments that did not. Moreover available, although incomplete, historic data from hospitals that could not be included in the study of secular trends due to changes in the catchment areas did not differ significantly from the main trend. Thus, although the historic data stem from a catchment area accounting for less than one half of the total population, we have found no evidence that they are not representative of the entire population. Another problem with the historic data is the lack of representation of major cities because here reorganisations of the catchment areas make population-based data hard to extract. However analysis of data from 1986 indicate similar rates for elective operations and operations for ulcer perforations in the major cities as in the population at large.

Another possibility is that the decline was confined to reoperations only, while the rate of first-time ulcer operations has remained on a steady level. The number of reoperations was, however, small during the entire period. Further during the past 30 years highly selective vagotomies have increasingly taken the place of resections as the method of choice in surgical treatment of duodenal ulcer and thus there has been a shift toward operations with higher recurrence rates. Therefore there is little reason for assuming that the number of reoperations would have declined substantially. On the contrary Gustavsson et al.[3] demonstrated an upward trend in reoperations.

The epidemiology of peptic ulcer disease has remained elusive. Ulcer symptomatology is often vague and unspecific and the disease is seldom life threatening. Therefore there is a significant fraction of the ulcer population that never seeks medical advice. Among those who see a doctor some are not given the benefit of a firm diagnosis. There is no simple and noninvasive method for determining the presence of ulcer disease in population surveys. Thus any attempt at estimation of the true incidence or prevalence rates will be hampered by an iceberg phenomenon that is more troublesome than in most other diseases. Despite these problems there is general, but not uniform, agreement that peptic ulcer disease is declining. In longitudinal population surveys, Pulvertaft,[6] Meade et al.,[7] and Mendeloff[8] reported falling incidence rates of duodenal ulcer, although Bonnevie[9,10] was unable to confirm any downward trend in Copenhagen for duodenal or gastric ulcers. In northern Norway, where there has been a marked predominance for gastric ulcers, duodenal ulcer rates seem to be increasing while gastric ulcer rates are falling.[11] There is also evidence from an American Health Maintenance Organization that outpatient episodes of duodenal ulcer, and to a lesser extent of gastric ulcer, have declined.[12] Changes in diagnostic activity could, however, have profound impact on such figures and it has been shown in Sweden that the total number of radiologic and endoscopic investigations of the stomach is slowly decreasing.[13]

Several authors have reported a decline in hospital admittance rates for uncomplicated duodenal ulcer, whereas the trend for gastric ulcer is less clear.[13-16] Those studies fail to distinguish between first-time admissions and readmissions, and a shift toward fewer readmissions could explain some of the decline. However surgical data reveal the same trend and the results of the present study closely agree with those obtained by others[3-5,14,15,17]: the marked decline seems indisputable, particularly in men with duodenal ulcer. There are also several reports of a decreasing peptic ulcer mortality rate,[4,16,18-21] although it seems as if the mortality rate in the United States has leveled off in recent years.[14] In the city of Malmö, Sweden, where the autopsy rate has been exceptionally high, Lindström[22] could not show any decline in peptic ulcer rate. One should keep in mind, however, that only a small fraction of all ulcer patients actually die of their disease.

There are good reasons for putting particular emphasis on trends in ulcer perforations, which probably reflect ulcer epidemiology better than elective surgery. First we can reasonably assume that perforations occur at random among those at risk, *i.e.*, those with active ulcers. There is little reason to believe that the risk for any one ulcer patient of being stricken with perforation has changed significantly over time. Thus the perforation rate probably runs parallel with the true ulcer prevalence rate and the former might serve as an index of the latter. Second because almost every individual with a perforation is admitted to a hospital, an iceberg effect is improbable. Third the dramatic clinical presentation almost inevitably leads to a firm diagnosis, making misclassification a minor problem. Moreover surgical treatment was used almost without exception in Sweden during the period under study, and thus the surgical rate is a good indicator of the perforation incidence.

The decline in perforation rate shown by us is also in keeping with results obtained by others.[23] It seems, however, that the trends for ulcer complications are different in different age groups. Whereas perforation rates are steeply falling for younger people, there seems to be an upward trend among the elderly, particularly older women with duodenal ulcer.[16,17,24] The age distribution in the study base of the present study, however, could not have changed to such extent that it would explain our findings, but changes in patient management may have. This involves the general trend toward a greater readiness to accept even very old people for surgery.[17] This factor partly may have concealed a true decline in ulcer perforations. Therefore our estimation of the downward trend is probably conservative.

Because the decline in elective operations is much greater than that in perforations, other factors must have added to a possible fall in incidence. One possible explanation is the better pharmacologic agents that have appeared, particularly the H_2-receptor antagonists. However cimetidine was not introduced until 1978 in Sweden and, as has been shown by Fineberg and Pearlman[4] and Wyllie et al.,[5] the impact of cimetidine on surgical rates seems to be brief and confined to the years immediately following its release.

Another important landmark in the history of peptic ulcer management is the advent of fiberoptic endoscopy. It is conceivable that modern endoscopy has had a particular impact on elective surgical rates for gastric ulcer because endoscopy often obviates the need for operation to rule out malignancy. However, as shown in Rochester, Minnesota, relatively few operations were in practice performed for this reason.[3] The impact of endoscopy on surgical rates could perhaps be explained by a greater precision in the diagnosis, which would lower the risk of falsely classifying cases of nonulcer dyspepsia as peptic ulcer. However neither better drugs nor more efficient diagnostic tools can account for the entire decline because the trend started already in the 1950s. The 50% decline in ulcer perforations suggests that true changes in ulcer prevalence has taken place, although there is of course a possibility that ulcers now tend to run a more benign course while the prevalence rate remains undiminished.

We can only speculate on the reason for the possible decline in ulcer prevalence. Among numerous hypotheses that have been forwarded, such as change in smoking habits, decreased physical work load, and diminished salt intake, recent emphasis has been focused on the bacterium Campylobacter pylori,[25] which appears to be a necessary cofactor for development of peptic ulcer disease. It is an attractive hypothesis that a change in infection panorama has contributed to the dramatic fluctuations that have been observed during the past century. Further studies of comparative epidemiology are needed to settle these questions.

We conclude that there has been a dramatic decline in peptic ulcer surgery in Sweden that started before the advent of fiberoptic endoscopy, H_2-receptor antagonists, and highly selective vagotomy. The falling incidence of perforations (−50%) suggests that the ulcer prevalence (or perhaps severity) has changed, but not as dramatically as would be suggested by the marked decrease in hospital admittance rates. The greater reduction of elective surgery, on the other hand, indicates that altered strategies for surgery play an important role as well. The small number of future elective operations for peptic ulcer disease suggests that we must place great emphasis on surgical training and organization of surgical care as we serve the few patients who need elective surgery at specialized centers.

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Curative Resection of Multiple Gastrinomas Aided by Selective Arterial Secretin Injection Test and Intraoperative Secretin Test

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Recently a number of surgeons have recommended radical resection of gastrinomas in Zollinger-Ellison syndrome (ZES). We have developed a useful technique for preoperative localization of gastrinomas—the selective arterial secretin injection test (SASI)—and we recommend an intraoperative secretin test (IOS) for deciding the radicality of resection of gastrinomas. Here the results of SASI and IOS tests in 11 patients with ZES are examined and compared with the results of other techniques. The SASI test localized gastrinomas in all of the patients, while the sensitivity of ultrasonography, computed tomography, arteriography, or portal venous blood samplings was between 1/11 and 5/11. On the basis of the results of the SASI test, radical resection of gastrinoma was performed in four patients (three pancreatoduodenectomies and one extirpation). After pancreatoduodenectomy, immunohistologic study of the specimen revealed multiple microgastrinomas and lymph node metastases in two patients and the coexistence of a microgastrinoma and a gastinoma in one patient. The IOS test was useful in the estimation of the advisability of radicality, and in two patients total gastrectomy was not performed because of the results of the IOS test. These four patients are well and have returned to work, and their serum gastrin levels are below 35 pg/mL. Thus we believe SASI and IOS tests are helpful for planning curative resection of gastrinomas.

RECENTLY RADICAL RESECTION of gastrinomas has been recommended by a number of surgeons.[1-3] We have described the usefulness of the selective arterial secretin injection test (SASI) and of the intraoperative secretin test (IOS) for surgical treatment of this tumor.[4,5] In eleven patients with Zollinger-Ellison syndrome (ZES), the SASI test was performed for preoperative localization, as were ultrasonography (US), computed tomography (CT), abdominal arteriography (SAG), and portal venous blood samplings (PVS). On the basis of the results of SASI tests, radical operation was performed in four patients. We report here the results of SASI tests, IOS tests, and surgery.

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Patients and Methods

Eleven patients with documented ZES were treated in our departments (Table 1). All of the patients had been treated for gastric ulcers (cases 4 and 5) or duodenal ulcers (the other nine patients) before admission to our clinic; two of them had previous total gastrectomy (cases 2 and 7) and five had previous partial gastrectomy (cases 5, 6, 9, 10, and 11). Tarry stool was noted at the time of admission in eight patients, but not in those who had previous total gastrectomy (cases 2 and 7) or in case 4. Anastomotic ulcers were demonstrated after admission in cases 3, 5, 6, 9, and 10. Criteria for the diagnosis of ZES were gastric hyperacidity, a serum gastrin concentration (IRG) more than 200 pg/mL (more than 100 pg/mL in patients who underwent antrectomies), and increase of serum gastrin (ΔIRG) more than 100 pg/mL after a bolus injection of secretin (3 U/kg) into a cubital vein. The secretin that was used in this study was Secrepan^R (Eizai Co., Ltd., Tokyo, Japan). Gastrinomas were located by US, CT, SAG, PVS, and SASI tests. The details of the SASI test have been listed elsewhere.[4] Briefly they are as follows. We inserted the tip of the catheter into an artery near the pancreas, such as the gastroduodenal artery, the splenic artery, or the superior mesenteric artery. Then we injected 20 to 30 U of secretin into the artery, took blood samples from the hepatic vein before and 20, 40, 60, 90, and 120 seconds after the injection of secretin, and measured the changes of hepatic venous (HV)IRG. When the secretin

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TABLE 1. *Patients with Zollinger–Ellison Syndrome*

			Gastric Juice		Secretin Test		Localization Test						
Case No.	Age (years)	Sex	BAO (mmol/hr)	BAO/ MAO	Basal IRG (pg/mL)	ΔIRG	US	CT	SAG	PVS	SASI	Treatment	Prognosis
1	35	F	31.3	0.97	2900	1,200	hep met	hep met, panc head	hep met, panc head	np	hep met, panc head	STZ, 5FU	2 years, died
2	47	M	Total gastrectomy		580	250	nl	nl	panc body	np	upper half of panc head or duod	Distal pancreatectomy	6 years, alive
3	53	M	Partial gastrectomy 2.03 (bile)	0.43	100	184	nl	nl	nl	np	upper half of panc head or duod	(1) Extir of a lymph node (2) Pancreato-duodenectomy	2 years, alive (IRG 30)
4	68	F	10.84	0.86	1200	230	nl	nl	nl	np	whole panc	cimetidine	6 years, alive
5	43	M	Partial gastrectomy —	—	733	312	nl	nl	panc head	np	upper half of panc head or duod	(1) SMS201-995 (2) Pancreato-duodenectomy	10 months, alive (IRG 23)
6	57	M	9.00	0.81	1200	350	panc head	nl	panc tail	nl	upper half of panc head or duod	cimetidine	1 year, alive
7	44	M	11.08	0.80	1018	375	nl	nl	nl	nl	upper half of panc head or duod	(1) Extir of a lymph node (2) Pancreato-duodenectomy	4 months, alive (IRG 30)
8	13	M	23.7	0.78	905	5666	panc head	panc head	nl	panc head or duod	upper half of panc head or duod	cimetidine	2 years, alive
9	40	F	66.4	0.99	1750	3810	panc head	panc head	nl	nl	upper half of panc head or duod	cimetidine	1 year, alive
10	62	F	51.4	0.71	12,500	30,500	panc body	panc body	panc body	nl	panc body & lt gast a area	Extir of a tumor	1 year, alive
11	50	F	30.1	0.85	400	200	nl	nl	nl	nl	upper half of panc head or duod	parathyroidectomy cimetidine	5 years, alive (IRG 120)

BAO: basal acid out put; MAO: maximum acid out put; SAG: selective arteriography; PVS: portal venous blood samplings; M: male; F: female; panc: pancreas; duod: duodenum; SASI: selective arterial secretin injection test; np: not performed; nl: not localized; lt gast a area: area fed by the left gastric artery; hep: hepatic; met: metastasis; ΔIRG: maximum increase of IRG after injection of 2 μ/kg of secretin; STZ: streptozotocin; Extir: extirpation.

is injected into a feeding artery of the gastrinoma, the HV-IRG rises more than 80 pg/mL within 40 seconds to at least 120% of the basal HV-IRG (Fig. 1).

The gastroduodenal artery feeds the upper half of the head of the pancreas and the upper duodenum. The splenic artery feeds the body and tail of the pancreas. The lower half of the head of the pancreas and the lower duodenum are fed by the inferior pancreatoduodenal artery, which is a branch of the superior mesenteric artery.[6] Thus we can first demonstrate feeders of functioning gastrinomas, and then we can locate the functioning gastrinoma(s).

The intraoperative secretin test is performed by the bolus intravenous injection of 3 U/kg of secretin.[5] Blood samples were taken from a cubital vein before and 2, 4, and 6 minutes after the injection of secretin. Rapid radioimmunoassay of serum IRG was performed by shortening the incubation time with antibody 1611 (a gift from Dr. J. H. Walsh, Los Angeles, CA) as described before; *i.e.*, the reaction mixtures were incubated for 1 hour at room temperature.[5]

As soon as the specimen was removed, the duodenum and pancreas were carefully palpated in a search for microgastrinomas in the duodenal wall, pancreas or the lymph nodes. Any suspected tumors or lymph nodes were fixed in both Bouin's solution and 10% formalin solution and embedded in paraffin. Paraffin sections were stained with Masson-Fontana, Grimelius, and Hellerstrom-Hellman silver stains. Immunohistochemical staining was done with either Sternberger's peroxidase antiperoxidase method or Nakane's indirect method.[7,8] Antisera prepared for this study were rabbit antigastrin serum (a gift from Professor N. Yanaihara, Shizuoka College of Pharmacy, Shizuoka, Japan), rabbit antiglucagon serum (Japan Immunoresearch Lab., Tokyo, Japan) and rabbit antibovine pancreatic peptide serum (a gift from Professor R. E. Chance, Eli Lilly Co., Indianapolis, IN).

Results

US, CT, SAG, and SASI tests were performed in all patients, and PVS was performed in six patients (Table 1). US, CT, and SAG were useful in the detection of liver metastases, but they were not useful in locating main gastrinomas; that is, US, CT, and SAG visualized tumors in and around the pancreas in 4, 4, and 5 patients, respectively. The diameters of the visualized tumors were between 1.5 and 5.0 cm. PVS was useful in only one patient. The SASI test localized functioning gastrinoma(s) in all patients. Case 1 had a large gastrinoma in the head of the pancreas and multiple hepatic metastases, which were identified by all diagnostic techniques. In case 2, SAG visualized a tumor in the body of the pancreas. This patient underwent a distal pancreatectomy. The resected tumor was not a gastrinoma, but a nonfunctioning tumor; that is, his serum IRG did not change at all after the operation and the resected tumor cells did not secrete gastrin into the culture medium, although 10% of the tumor cells were stained with antigastrin serum. One year later, the SASI test located functioning gastrinomas in the upper part of the pancreas and the upper duodenum in this patient. His serum IRG is now 4500 pg/mL.

The results of the SASI test in the other patients (cases 3 to 11) are shown in Table 2. The increase of HV-IRG 40 seconds after the injection of secretin into each artery above the basal IRG (ΔIRG_{40}) was calculated. The ratio of the percentage of IRG_{40} to the basal HV-IRG ($\%\Delta IRG_{40}$) was also calculated. We determined that an artery was a feeder of a functioning gastrinoma when the ΔIRG_{40} was more than 80 pg/mL and the $\%\Delta IRG_{40}$ was more than 20%. In six patients who were examined at surgery or autopsy, the results of the SASI test were correct.

In three patients (cases 3, 5, and 7), pancreatoduodenectomy was performed on the basis of the results of the SASI test, which identified gastrinomas located in the upper half of the head of the pancreas or duodenum, but not in the tail or body of the pancreas. We resected the head of the pancreas, the duodenum, and the gallbladder, cleaning out the lymph nodes around the pancreas even when we could not detect any tumors or any positive lymph nodes. In each resected specimen, multiple gastrinomas were detected by immunohistologic examination as shown in Figures 2 to 4. Two patients had lymph node metastasis. They are well and have returned to work after operation. Their serum IRG levels have been less than 30 pg/mL during their postoperative courses of 4 months to 2 years. These patients do not have multiple endocrine adenomatosis type I. In case 3, there were 2 microgastrinomas that measured 5 mm in diameter in the duodenal wall, 8 microgastrinomas in the parenchyma of the head of the pancreas, and 1 metastatic lymph node[4] (Fig. 1). Details of cases 5 and 7 will be described as case reports.

In one patient (case 10), the SASI test showed gastrinomas in the area fed by the left gastric artery and the splenic artery but not in the head of the pancreas or in the duodenum. Laparotomy revealed a tumor in the lesser omentum fed by branches of the left gastric artery and of the splenic artery. The tumor was extirpated and her serum IRG is less than 40 pg/mL. Two patients (cases 6 and 8) are waiting for operation.

Case Reports

Case 7

This 44-year-old man had been treated with 800 mg/day of cimetidine for 3 years when he developed perforation of his duodenal ulcer and underwent an emergency partial gastrectomy on February 22, 1987. The massive postoperative output of gastric juice (more than 2 L per day) and the high serum IRG level of 606.9 pg/mL, as well as a positive

TABLE 2. *Results of Selective Arterial Secretion Injection Test*

Case No.	Age	Sex	Artery	IRG (pg/mL)		ΔIRG_{40} (pg/mL)	$\%\Delta IRG_{40}$	Feeding Arteries	Surgery
				Basal	40 sec				
3	53	M	GDA	97	227	130	134.0	GDA	PD
			SMA	96	124	28	29.2		
			SPA	97	93	−4	−4.1		
4	68	F	GDA	242	368	126	52.1	GDA, SMA SPA	—
			SMA	249	403	154	61.8		
			SPA	273	386	113	41.4		
5	43	M	GDA	467	624	157	33.6	GDA	PD
			SMA	888	814	−74	−8.3		
			DPA	574	544	33	5.7		
			SPA	606	639	33	5.5		
6	57	M	GDA	2396	3638	1242	51.8	GDA & SMA	—
			SMA	1125	1542	417	37.1		
			SPA	1951	1932	−19	−1.0		
7	44	M	GDA	151	244	93	61.6	GDA	PD
			SMA	96	94	−2	−2.1		
			SPA	97	97	0	0		
8	13	M	GDA	1446	6996	5550	383.8	GDA	—
			SMA	3600	3462	−138	−4.9		
			SPA	2826	2364	−462	−12.8		
9	40	F	GDA	2335	3430	1095	46.9	GDA	—
			SMA	3200	3390	190	5.9		
			SPA	2145	2335	190	8.9		
10	62	F	GDA	20,500	18,700	−1800	−8.9	LGA & SPA	Extir
			LGA	13,400	22,700	9300	69.4		
			SPA	16,200	31,900	15,700	97.0		
11	50	F	GDA	130	234	104	80.0	GDA & SMA	—
			SMA	133	287	154	115.8		
			SPA	143	155	12	8.4		

M: male; F: female; GDA: gastroduodenal artery; DPA: dorsal pancreatic artery; SMA: superior mesenteric artery; SPA: splenic artery; LGA: left gastric artery; $\Delta IRG_{40} = IRG_{40} - \text{Basal } IRG$; PD: pancreatoduodenectomy; Extir: Extirpation; $\%\Delta IRG_{40} = \dfrac{\Delta IRG_{40} \times 100}{\text{Basal IRG}}$.

secretin test, confirmed the diagnosis of ZES. None of the diagnostic imaging techniques used (US, CT, and SAG) could demonstrate a tumor, and PVS also could not localize a gastrinoma. On April 7, 1987, surgeons opened his abdomen to search for a gastrinoma and found a metastatic lymph node on the surface of the head of the pancreas. Frozen sections were diagnosed as carcinoidlike tumor that was confirmed after operation by immunohistochemical study to be a metastatic lymph node from a gastrinoma. The main gastrinoma was not found and a total gastrectomy was performed. He was then transferred to Kyoto University Hospital for SASI testing.

The results of the SASI test are shown in Figure 5. The increase of HV-IRG(ΔIRG_{40}) from the basal level was 100 pg/mL 40 seconds after the injection of 25 U of secretin into the gastroduodenal artery, although ΔIRG_{40} was 2 pg/mL and 0 pg/mL after the injection of the same dose of secretin into the splenic artery and the superior mesenteric artery, respectively. This significant difference led us to conclude that functioning gastrinomas were present in the upper part of the head of the pancreas or duodenum. On July 5, 1988, we performed a pancreatoduodenectomy with cleaning of the lymph nodes, although we could not identify any gastrinomas in the head of the pancreas or in the duodenum during the operation. Intraoperative secretin test performed immediately after the pancreatoduodenectomy was negative, that is, IRG(pg/mL) was 82.3, 80.1, 75.0, and 75.8, before and 2, 4, and 6 minutes after the injection of 3 U/kg of secretin into a cubital vein (Fig. 6). Thus we confirmed the completeness of the resection and closed his abdomen. Eight hours after the resection serum IRG became 27 pg/mL. His postoperative course was uneventful and he was discharged 4 weeks later. He is well and back at work. A secretin test on November 1, 1988 was negative; that is, IRG(pg/mL) was 25, 26, 23, and 22, before and 2, 4, and 6 minutes, respectively, after the injection of 3 U/kg of Secrepan^{R} into a cubital vein. Pathologic examination of the resected specimen revealed a microgastrinoma that measured 4 mm in diameter in the duodenal submucosa and three metastatic lymph nodes (Fig. 7). A metastatic lymph node had been extirpated before, so he had had four metastatic lymph nodes around the head of the pancreas (Fig. 2).

Case 5

This 43-year-old man had been treated medically for a gastric ulcer for 6 years when he underwent a partial gastrectomy on April 23, 1984. Six months after operation epigastralgia recurred and medical treatment was required again. On November 25 he visited Yukawa Gastrointestinal Disease Hospital in Osaka and was found to have hypergastrinemia of more than 150 pg/mL. US and CT could not visualize a tumor, so he was transferred to Kyoto University Hospital for SASI testing on January 14, 1988. The results of the SASI test are shown in Figure 8 and Table

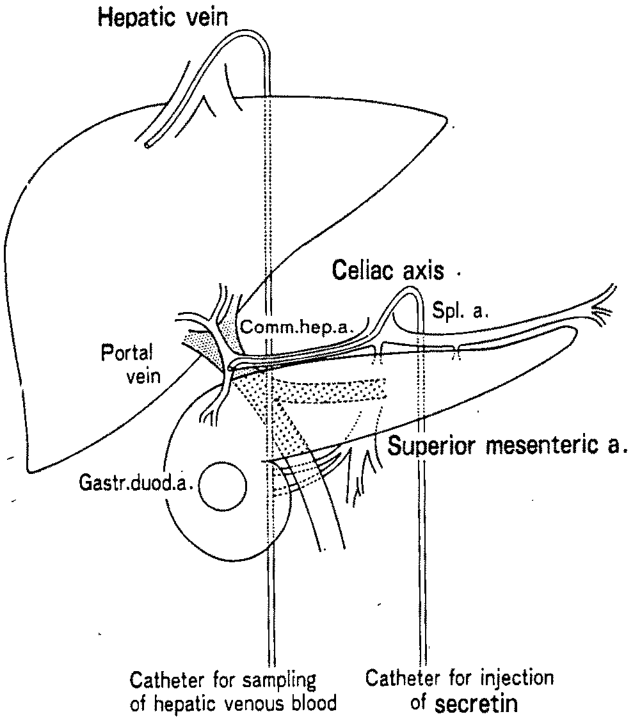

FIG. 1. Diagram of SASI test. Secretin was injected into the gastroduodenal artery, the splenic artery or the superior mesenteric artery through the tip of a catheter for arteriography. Then hepatic blood was sampled every 20 seconds three times and 90 seconds after the injection of secretin.

1. HV-IRG rose more than 150 pg/mL 40 seconds after the injection of 30 U of secretin into the gastroduodenal artery, but did not change for 60 seconds after the injection of the same dose of secretin into either the dorsal pancreatic artery or the splenic artery. A rise of HV-IRG two minutes after injection of secretin into the splenic artery is due to the stimulation of gastrinomas located in an area other than the body or tail of the pancreas with release of gastrin in response to the second circulation of secretin. The ΔIRG_{40} after the injection of secretin into the gastroduodenal artery was 175 pg/mL, although it was −40 pg/mL and 5 pg/mL after the injection of secretin into the dorsal pancreatic artery and the splenic artery, respectively.

This significant difference led us to diagnose gastrinomas located in the feeding area of the gastroduodenal artery, *i.e.*, the upper part of the head of the pancreas or the upper duodenum and not in the body or tail

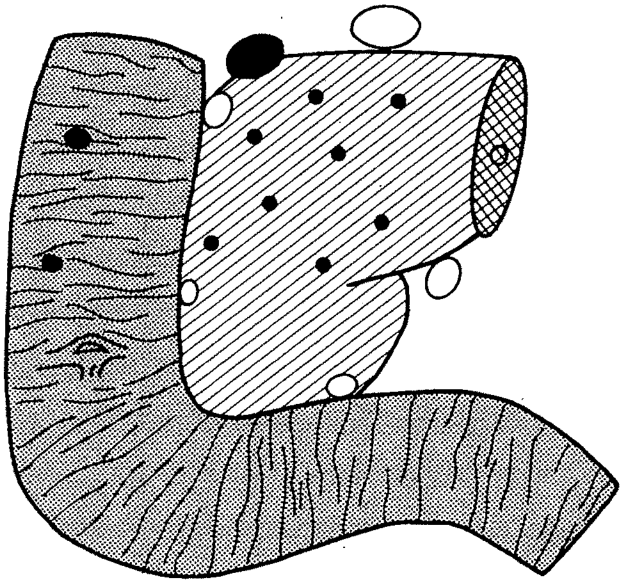

FIG. 2. Location of multiple gastrinomas in case 3. Immunohistochemical study revealed 2 duodenal microgastrinomas, 8 intrapancreatic microgastrinomas, and 1 metastatic lymph node on the upper edge of the head of the pancreas. None of them could be identified during the operation. Two duodenal microgastrinomas were palpable in the specimen but could not be identified macroscopically as gastrinomas.

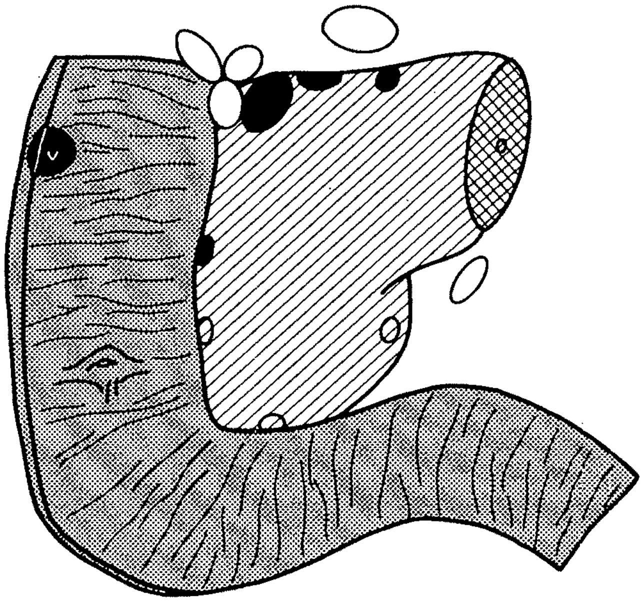

FIG. 3. Location of gastrinomas in case 7. One duodenal microgastrinoma was located 1 cm anal from the stump of the duodenum. Four metastatic lymph nodes were detected in the upper half of the head of the pancreas.

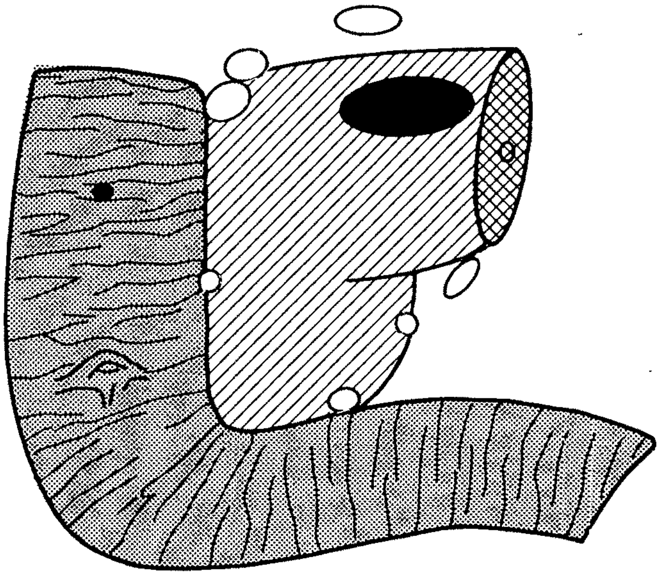

FIG. 4. Location of gastrinomas in case 5. One intrapancreatic gastrinoma was palpable during the operation, but one duodenal microgastrinoma was revealed by postoperative immunohistochemical study.

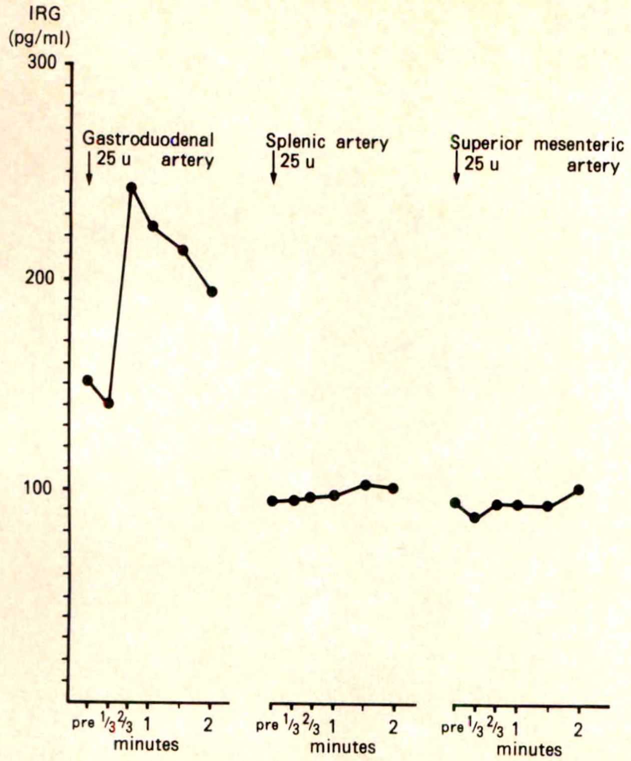

FIG. 5. Results of SASI test in case 7. HV-IRG was increased 40 seconds after the injection of 25 U of secretin into the gastroduodenal artery, but it did not change for 60 seconds after the injection of secretin into the splenic artery or the superior mesenteric artery.

of the pancreas. Superselective arteriography through the gastroduodenal artery demonstrated a hypervascular tumor in the head of the pancreas.

On January 21, 1988, surgery was performed. A tumor that had been demonstrated by SAG was palpable in the head of the pancreas and thus we performed a pancreatoduodenectomy. Intraoperative secretin test performed with 3 U/kg of secretin was negative; that is, serum IRG(pg/mL) was 228.0, 194.8, 201.0, and 204.1 before and 2, 4, and 6 minutes after the injection of secretin, respectively. Thus we could confirm that all functioning gastrinomas had been resected. The pathologic study of the specimen revealed a minute gastrinoma in the duodenal submucosa in addition to the gastrinoma palpated during the operation. No metastatic lymph nodes were found (Fig. 4). After operation he complained of left hypochondralgia and abdominal fullness. An upper gastrointestinal barium study revealed narrowing of the proximal jejunum. We opened his abdomen on February 18, 1988, and found the jejunum adherent to the abdominal wall, which was well separated. He was discharged 3 weeks later. He is well and has returned to work. His serum IRG is less than 35 pg/mL.

Discussion

Preoperative localization of gastrinoma in patients with ZES is often difficult.[2,3,9] It is not unusual for gastrinomas to be multiple and to coexist with nonfunctioning endocrine tumors.[10] The sensitivity of US, CT, and SAG has been reported to be between 40% and 70%.[2,3,11,12] In our study these techniques were useful in locating hepatic metastases, but the number of main tumors visualized was low; SAG gave the best results (5 of 11). In the three resected specimens of the head of the pancreas and the duodenum after pancreatoduodenectomy, immunohistologic study revealed 18 gastrinomas (including metastatic lymph nodes), of which only two tumors had been demonstrated by preoperative diagnostic imaging techniques, and these could not show whether a visualized tumor was a functioning gastrinoma. Therefore we must conclude that these techniques are not adequate for the preoperative localization of gastrinomas and the decision of whether radical resection is indicated. The usefulness of PVS has been discussed many times, but is still controversial.[2,9-11] Good results of superselective catheterization into a branch of the portal vein near the pancreas have been reported.[12] But the results of our study were poor. We think that PVS does not provide clear data, and it is technically difficult.

The SASI test is easy if the tip of the catheter can be inserted selectively into the gastroduodenal artery, the splenic artery, or the superior mesenteric artery. Each study ends within two minutes after the injection of se-

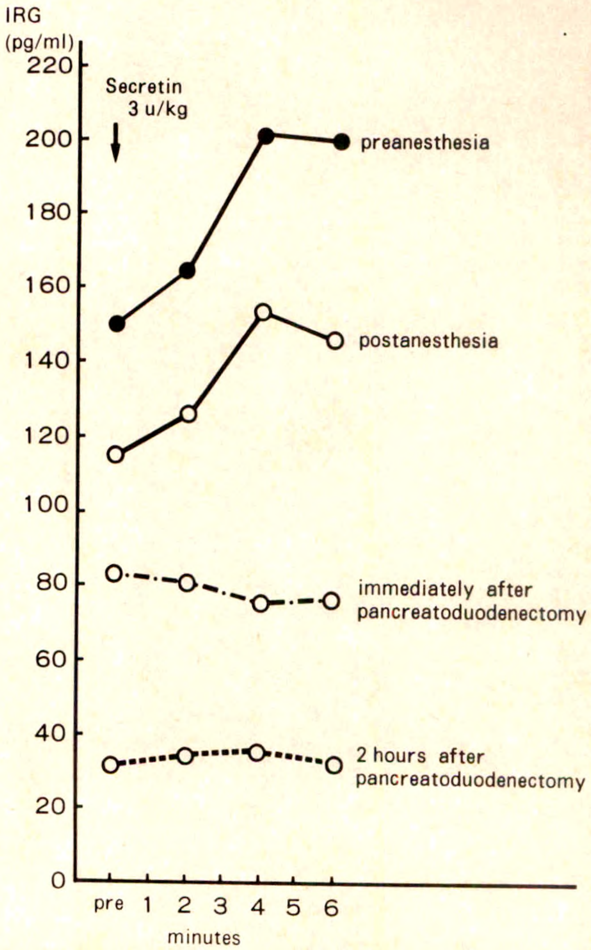

FIG. 6. Case 7. The intravenous secretin test was positive before and after general anesthesia but became negative after pancreatoduodenectomy. Thus we could confirm the completeness of the resection during the operation.

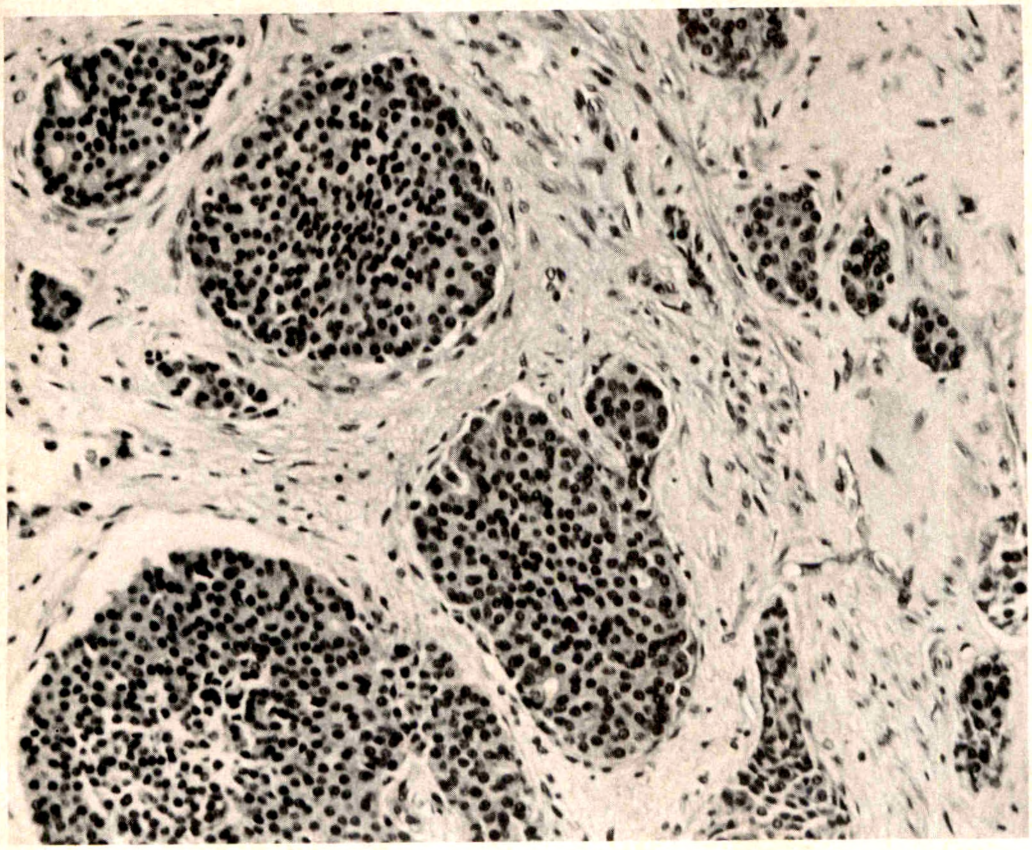

FIG. 7. Microscopic appearance of the duodenal submucosal microgastrinoma in case 7. Tumor cells with cellular atypism form solid nests that vary in size and shape and show invasive growing. (Hematoxylin and eosin, ×428)

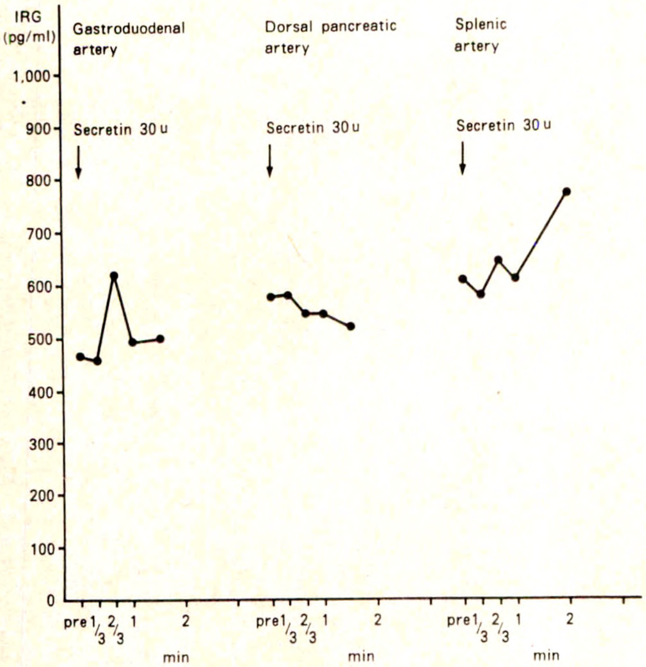

FIG. 8. Results of SASI test in case 5. HV-IRG rose 40 seconds after the injection of 30 U of secretin into the gastroduodenal artery but it did not change for 60 seconds after the injection of secretin into the dorsal pancreatic or the splenic artery. The rise of HV-IRG 90 seconds after the injection of secretin into the splenic artery is believed to be due to the stimulation of a gastrinoma in the head of the pancreas or the duodenum to release gastrin at the second circulation.

cretin into an artery near the pancreas.[4] It is easy to determine which arteries feed the gastrinoma if one makes a graph of the changes of HV-IRG as in Figures 5 and 7 and compares the rise of HV-IRG after the injection of secretin into a different artery. If an artery is a feeder, HV-IRG rises significantly within 40 seconds, but if an artery is not a feeder HV-IRG does not change for 60 seconds. Table 2 shows our calculations of ΔIRG_{40} and $\%\Delta IRG_{40}$ and our criteria for a feeder of gastrinomas; that is, if ΔIRG_{40} is more than 80 pg/mL and $\%\Delta IRG_{40}$ is more than 20%, the artery is a feeder. These criteria are useful when microgastrinomas are present in the duodenal wall or when a large gastrinoma is present in the lesser omentum.

In this series the SASI test localized gastrinomas in all of the patients. In most cases in which tumor stains were demonstrated by diagnostic imaging techniques, the SASI test also showed the existence of gastrinomas in the same area. But in two patients (cases 2 and 6) the visualized tumor was diagnosed not to be a functioning gastrinoma by the SASI test. In case 2, SAG showed a tumor in the tail of the pancreas and a distal pancreatectomy was performed, although the SASI test did not indicate that there was a functioning gastrinoma in the body or tail of the pancreas. The resected tumor was not a functioning gastrinoma, but a nonfunctioning endocrine tumor. The

SASI test performed 1 year after the operation localized gastrinomas in the upper part of the head of the pancreas or the upper duodenum. In case 6, SAG demonstrated a tumor, but the SASI test localized gastrinomas in the upper part of the head of the pancreas or duodenum. The tumor visualized in the hilar portion of the spleen seems to be an accessory spleen. We are preparing to perform a pancreatoduodenectomy in this case.

In four patients who had radical resections of gastrinomas, localization by the SASI test was correct and useful. In case 10 there was a single large gastrinoma in the lesser omentum and extirpation seems to have been curative. In the other three patients who underwent pancreatoduodenectomies (cases 3, 5, and 7) there were multiple microgastrinomas in the duodenum or the head of the pancreas and in two of them there were lymph node metastases. These results suggest the necessity of pancreatoduodenectomy when the SASI test shows that a gastrinoma is located in the head of the pancreas or in the duodenum.

Recently a few authors have reported that in patients with severe peptic ulcer symptoms, sometimes leading to death, duodenal microgastrinomas were found only at autopsy or surgery.[13,14] They speculated that in many ZES patients it is not diagnosed because no tumor is found during surgery. Two of our patients (cases 3 and 5) with microgastrinomas that were not found at the first operation developed anastomotic jejunal ulcers after operation, despite cimetidine treatment. Thus occult gastrinomas in ZES are not always asymptomatic or benign.[13-15] Zollinger reported that five of eight patients in whom no gross tumor was found at operation survived more than 10 years.[16] We believe that the SASI and IOS tests will help to raise the survival rate of such patients.

A few authors have recommended aggressive treatment for duodenal gastrinomas with or without lymph node involvement and have reported excellent clinical results after surgery.[17-19] Lander treated a patient who has been asymptomatic for 2.5 years after the extirpation of a minute duodenal submucosal gastrinoma and three metastatic lymph nodes.[20] We deliberated carefully before deciding to perform a pancreatoduodenectomy on the first patient (case 3); we opened the duodenum first, examined its interior carefully, and took a biopsy of an elevated area near the duodenal stump, which showed no pathologic abnormality. No gastrinoma was found during surgery, and we performed Whipple operation, believing the results of the SASI test. Immunohistologic study of the resected specimen revealed 2 minute submucosal gastrinomas, 1 metastatic lymph node, and 8 microgastrinomas in the head of the pancreas. He has been asympomatic for the 2 years since surgery. This experience has led us to conclude that it is very difficult to search for small duodenal or pancreatic gastrinomas or metastatic lymph nodes during surgery. If the IOS test is not negative after extirpation of a few gastrinomas in the head of the pancreas or the duodenum but the SASI test points to the presence of gastrinomas in the feeding area of the gastroduodenal artery, Whipple operation should be performed for curative resection of potentially malignant gastrinomas.[1,9]

Whipple operation for the resection of gastrinomas has been performed in relatively few institutions, and the results show considerable variation.[4,9,12] We believe that pancreatoduodenectomy in patients with gastrinomas should be performed just as in those with cancer of the head of the pancreas because of the high gastrinoma malignancy rate.[1-3] The postoperative mortality rate after pancreatoduodenectomy for pancreatic cancer is quite different in various reports. In our department it has been 0% for the past 3 years. Thus we have not found any reason not to perform pancreatoduodenectomy when the SASI test indicates the presence of gastrinomas in the head of the pancreas or in the duodenum. Three patients who underwent pancreatoduodenectomy recovered without complications and their serum IRG has been less than 30 pg/mL during their postoperative courses of four months and 2 years.

In patients with ZES whose stomachs have not been totally resected, we must decide whether the residual stomach should be resected after the removal of the gastrinomas. If we can confirm the radicality of the resection at the time of the operation, we can save the stomach. We believe that the IOS test is useful in the estimation of the radicality of the resection because the results of the IOS tests with rapid radioimmunoassay of serum gastrin in three patients were not different from those of the postoperative secretin test. On the basis of the results of the IOS test we did not resect the residual stomach in case 5, whose serum IRG remains less than 35 pg/mL after operation and whose secretin test (3 U/kg) is negative.

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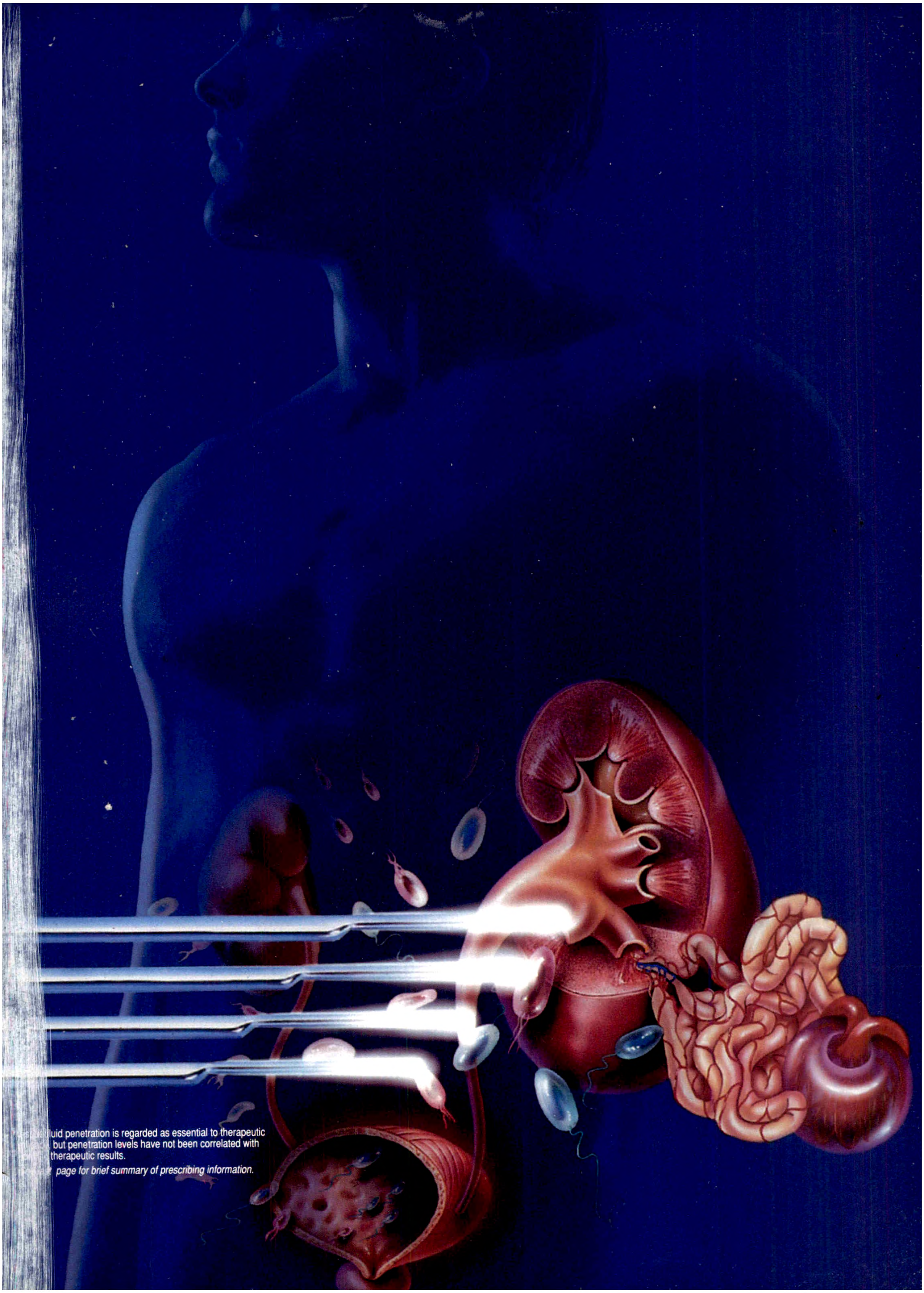

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Bone and Joint Infections caused by *Enterobacter cloacae*, *Serratia marcescens*, and *Pseudomonas aeruginosa*.

Urinary Tract Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Serratia marcescens*, *Proteus mirabilis*, *Providencia rettgeri*, *Morganella morganii*, *Citrobacter diversus*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Staphylococcus epidermidis*, and *Streptococcus faecalis*.

Infectious Diarrhea caused by *Escherichia coli* (enterotoxigenic strains), *Campylobacter jejuni*, *Shigella flexneri*,* and *Shigella sonnei** when antibacterial therapy is indicated.

*Efficacy for this organism in this organ system was studied in fewer than 10 infections.

CONTRAINDICATIONS

A history of hypersensitivity to ciprofloxacin is a contraindication to its use. A history of hypersensitivity to other quinolones may also contraindicate the use of ciprofloxacin.

WARNINGS

CIPROFLOXACIN SHOULD NOT BE USED IN CHILDREN, ADOLESCENTS, OR PREGNANT WOMEN. The oral administration of ciprofloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related drugs such as nalidixic acid, cinoxacin, and norfloxacin also produced erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species (SEE ANIMAL PHARMACOLOGY SECTION IN FULL PRESCRIBING INFORMATION).

PRECAUTIONS

General: As with other quinolones, ciprofloxacin may cause central nervous system (CNS) stimulation, which may lead to tremor, restlessness, lightheadedness, confusion, and rarely to hallucinations or convulsive seizures. Therefore, ciprofloxacin should be used with caution in patients with known or suspected CNS disorders, such as severe cerebral arteriosclerosis or epilepsy, or other factors which predispose to seizures (SEE ADVERSE REACTIONS).

Anaphylactic reactions following the first dose have been reported in patients receiving therapy with quinolones. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial edema, dyspnea, urticaria, and itching. Only a few patients had a history of hypersensitivity reaction. Anaphylactic reactions may require epinephrine and other emergency measures. Ciprofloxacin should be discontinued at the first sign of hypersensitivity or allergy.

Severe hypersensitivity reactions characterized by rash, fever, eosinophilia, jaundice, and hepatic necrosis with fatal outcome have been reported rarely (less than one per million prescriptions) in patients receiving ciprofloxacin along with other drugs. The possibility that these reactions were related to ciprofloxacin cannot be excluded. Ciprofloxacin should be discontinued at the first appearance of a skin rash or any sign of other hypersensitivity reaction.

Crystals of ciprofloxacin have been observed rarely in the urine of human subjects but more frequently in the urine of laboratory animals (SEE ANIMAL PHARMACOLOGY SECTION IN FULL PRESCRIBING INFORMATION). Crystalluria related to ciprofloxacin has been reported only rarely in man, because human urine is usually acidic. Patients receiving ciprofloxacin should be well hydrated, and alkalinity of the urine should be avoided. The recommended daily dose should not be exceeded.

Alteration of the dosage regimen is necessary for patients with impairment of renal function (SEE DOSAGE AND ADMINISTRATION).

As with any potent drug, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic function, is advisable during prolonged therapy.

Drug Interactions: As with other quinolones, concurrent administration of ciprofloxacin with theophylline may lead to elevated plasma concentrations of theophylline and prolongation of its elimination half-life. This may result in increased risk of theophylline-related adverse reactions. If concomitant use cannot be avoided, plasma levels of theophylline should be monitored and dosage adjustments made as appropriate.

Quinolones, including ciprofloxacin, have also been shown to interfere with the metabolism of caffeine. This may lead to reduced clearance of caffeine and a prolongation of its plasma half-life.

Antacids containing magnesium hydroxide or aluminum hydroxide may interfere with the absorption of ciprofloxacin resulting in serum and urine levels lower than desired; concurrent administration of these agents with ciprofloxacin should be avoided.

Concomitant administration of the nonsteroidal anti-inflammatory drug fenbufen with a quinolone has been reported to increase the risk of CNS stimulation and convulsive seizures.

Probenecid interferes with the renal tubular secretion of ciprofloxacin and produces an increase in the level of ciprofloxacin in the serum. This should be considered if patients are receiving both drugs concomitantly.

As with other broad-spectrum antibiotics, prolonged use of ciprofloxacin may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition and microbial susceptibility testing is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Information for Patients: Patients should be advised that ciprofloxacin may be taken with or without meals. The preferred time of dosing is two hours after a meal. Patients should also be advised to drink fluids liberally and not take antacids containing magnesium or aluminum.

Patients should be advised that ciprofloxacin may be associated with hypersensitivity reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash or other allergic reaction.

Ciprofloxacin may cause dizziness or lightheadedness; therefore patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or coordination.

Patients should be advised that ciprofloxacin may increase the effects of theophylline and caffeine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Eight in vitro mutagenicity tests have been conducted with ciprofloxacin and the test results are listed below:

Salmonella/Microsome Test (Negative)
E. coli DNA Repair Assay (Negative)
Mouse Lymphoma Cell Forward Mutation Assay (Positive)
Chinese Hamster V_{79} Cell HGPRT Test (Negative)
Syrian Hamster Embryo Cell Transformation Assay (Negative)
Saccharomyces cerevisiae Point Mutation Assay (Negative)
Saccharomyces cerevisiae Mitotic Crossover and Gene Conversion Assay (Negative)
Rat Hepatocyte DNA Repair Assay (Positive)

Thus, two of the eight tests were positive, but the results of the following three *in vivo* test systems gave negative results:

Rat Hepatocyte DNA Repair Assay
Micronucleus Test (Mice)
Dominant Lethal Test (Mice)

Long-term carcinogenicity studies in rats and mice have been completed. After daily oral dosing for up to 2 years, there is no evidence that ciprofloxacin had any carcinogenic or tumorigenic effects in these species.

Pregnancy—Pregnancy Category C: Reproduction studies have been performed in rats and mice at doses up to 6 times the usual daily human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ciprofloxacin. In rabbits, as with most antimicrobial agents, ciprofloxacin (30 and 100 mg/kg orally) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion. No teratogenicity was observed at either dose. After intravenous administration, at doses up to 20 mg/kg, no maternal toxicity was produced, and no embryotoxicity or teratogenicity was observed. There are, however, no adequate and well-controlled studies in pregnant women. SINCE CIPROFLOXACIN, LIKE OTHER DRUGS IN ITS CLASS, CAUSES ARTHROPATHY IN IMMATURE ANIMALS, IT SHOULD NOT BE USED IN PREGNANT WOMEN (SEE WARNINGS).

Nursing Mothers: It is not known whether ciprofloxacin is excreted in human milk; however, it is known that ciprofloxacin is excreted in the milk of lactating rats and that other drugs of this class are excreted in human milk. Because of this and because of the potential for serious adverse reactions from ciprofloxacin in nursing infants, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Patients under the age of 18 were not included in the clinical trials of ciprofloxacin because ciprofloxacin as well as other quinolones causes arthropathy in immature animals. Ciprofloxacin should not be used in children or adolescents (SEE WARNINGS).

ADVERSE REACTIONS

Ciprofloxacin is generally well tolerated. During clinical investigation, 2,799 patients received 2,868 courses of the drug. Adverse events that were considered likely to be drug related occurred in 7.3% of courses, possibly related in 9.2%, and remotely related in 3.0%. Ciprofloxacin was discontinued because of an adverse event in 3.5% of courses, primarily involving the gastrointestinal system (1.5%), skin (0.6%), and central nervous system (0.4%). Those events typical of quinolones are italicized.

The most frequently reported events, drug related or not, were *nausea* (5.2%), *diarrhea* (2.3%), *vomiting* (2.0%), *abdominal pain/discomfort* (1.7%), *headache* (1.2%), *restlessness* (1.1%), and *rash* (1.1%).

Additional events that occurred in less than 1% of ciprofloxacin courses are listed below.

GASTROINTESTINAL: *(See above)*, painful oral mucosa, oral candidiasis, dysphagia, intestinal perforation, gastrointestinal bleeding.

CENTRAL NERVOUS SYSTEM: *(See above), dizziness, lightheadedness, insomnia, nightmares, hallucinations, manic reaction, irritability, tremor, ataxia, convulsive seizures, lethargy, drowsiness, weakness, malaise, anorexia, phobia, depersonalization, depression, paresthesia.*

SKIN/HYPERSENSITIVITY: *(See above), pruritus, urticaria, photosensitivity, flushing, fever, chills, angioedema, edema of the face, neck, lips, conjunctivae or hands*, cutaneous candidiasis, hyperpigmentation, erythema nodosum.

Allergic reactions ranging from urticaria to anaphylactic reactions have been reported (SEE PRECAUTIONS).

SPECIAL SENSES: *blurred vision, disturbed vision (change in color perception, overbrightness of lights), decreased visual acuity, diplopia, eye pain, tinnitus, hearing loss, bad taste.*

MUSCULOSKELETAL: *joint or back pain, joint stiffness*, achiness, neck or chest pain, flare-up of gout.

RENAL/UROGENITAL: *interstitial nephritis, nephritis, renal failure*, polyuria, urinary retention, urethral bleeding, vaginitis, acidosis.

CARDIOVASCULAR: palpitations, atrial flutter, ventricular ectopy, syncope, hypertension, angina pectoris, myocardial infarction, cardiopulmonary arrest, cerebral thrombosis.

RESPIRATORY: epistaxis, laryngeal or pulmonary edema, hiccough, hemoptysis, dyspnea, bronchospasm, pulmonary embolism.

Most of the adverse events reported were described as only mild or moderate in severity, abated soon after the drug was discontinued, and required no treatment.

In several instances, nausea, vomiting, tremor, restlessness, agitation, or palpitations were judged by investigators to be related to elevated plasma levels of theophylline possibly as a result of a drug interaction with ciprofloxacin.

Other adverse events reported in the postmarketing phase include anaphylactoid reactions, Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, hepatic necrosis, postural hypotension, possible exacerbation of myasthenia gravis, confusion, dysphasia, nystagmus, pseudomembranous colitis, dyspepsia, flatulence, and constipation. Also reported were agranulocytosis; elevation of serum triglycerides, serum cholesterol, blood glucose, serum potassium; prolongation of prothrombin time; albuminuria; candiduria, vaginal candidiasis; and renal calculi (SEE PRECAUTIONS).

Adverse Laboratory Changes: Changes in laboratory parameters listed as adverse events without regard to drug relationship:

Hepatic—Elevations of: ALT (SGPT) (1.9%), AST (SGOT) (1.7%), alkaline phosphatase (0.8%), LDH (0.4%), serum bilirubin (0.3%).

Cholestatic jaundice has been reported.

Hematologic—Eosinophilia (0.6%), leukopenia (0.4%), decreased blood platelets (0.1%), elevated blood platelets (0.1%), pancytopenia (0.1%).

Renal—Elevations of: Serum creatinine (1.1%), BUN (0.9%).

CRYSTALLURIA, CYLINDRURIA, AND HEMATURIA HAVE BEEN REPORTED.

Other changes occurring in less than 0.1% of courses were: Elevation of serum gammaglutamyl transferase, elevation of serum amylase, reduction in blood glucose, elevated uric acid, decrease in hemoglobin, anemia, bleeding diathesis, increase in blood monocytes, and leukocytosis.

OVERDOSAGE

Information on overdosage in humans is not available. In the event of acute overdosage, the stomach should be emptied by inducing vomiting or by gastric lavage. The patient should be carefully observed and given supportive treatment. Adequate hydration must be maintained. Only a small amount of ciprofloxacin (<10%) is removed from the body after hemodialysis or peritoneal dialysis.

DOSAGE AND ADMINISTRATION

The usual adult dosage for patients with urinary tract infections is 250 mg every 12 hours. For patients with complicated infections caused by organisms not highly susceptible, 500 mg may be administered every 12 hours.

Lower respiratory tract infections, skin and skin structure infections, and bone and joint infections may be treated with 500 mg every 12 hours. For more severe or complicated infections, a dosage of 750 mg may be given every 12 hours.

The recommended dosage for infectious diarrhea is 500 mg every 12 hours.

In patients with renal impairment, some modification of dosage is recommended (SEE DOSAGE AND ADMINISTRATION SECTION IN FULL PRESCRIBING INFORMATION).

HOW SUPPLIED

Cipro® (ciprofloxacin HCl/Miles) is available as tablets of 250 mg, 500 mg, and 750 mg in bottles of 50, and in Unit-Dose packages of 100 (SEE FULL PRESCRIBING INFORMATION FOR COMPLETE DESCRIPTION).

References: 1. Data on file, Miles Inc, Pharmaceutical Division. **2.** *Physicians' Desk Reference®*. 43rd ed. Oradell, NJ: Medical Economics Co Inc; 1989:891, 1376, 1441, 1486, 1724, 1779. **3.** Barry AL, et al. Antibacterial activities of ciprofloxacin, norfloxacin, oxolinic acid, cinoxacin, and nalidixic acid. *Antimicrob Agents Chemother*. 1984;25:633-637. **4.** Borner K, et al. Pharmacokinetics of ciprofloxacin in healthy volunteers after oral and intravenous administration. *Eur J Clin Microbiol*. 1986;5:179-186. **5.** Gombert ME, et al. Levels of ciprofloxacin in prostatic tissue of patients undergoing prostatectomy. *Rev Infect Dis*. 1988;10(suppl 1):S169. **6.** *Medi-Span® Hospital Formulary Pricing Guide*. June 1989:9,35.

***Achieves 97% favorable clinical response (resolution + improvement) of infections due to susceptible strains of indicated pathogens. See indicated organisms in prescribing information.**

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A Long-Term Randomized Prospective Trial of the Nissen Procedure *Versus* a Modified Toupet Technique

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Thirty-one patients about to undergo surgery for gastroesophageal reflux were randomized into either a Nissen fundoplication group (12) or a modified Toupet semifundoplication group (19). All patients were followed on a long-term basis for 5 years with a standard questionnaire, endoscopy, and manometry. Ninety-five per cent of the patients in the modified Toupet group had good or excellent results *versus* 67% for the Nissen group. However both procedures are effective in curtailing esophagitis with an improvement of the endoscopic grading in the Nissen group by 91% and 89% in the group undergoing the modified Toupet procedure. A significant improvement in symptoms (acid regurgitation, heartburn, retrosternal pain) was noted in both groups, except for dysphagia in the Nissen group. Three patients with a Nissen fundoplication had a slipped Nissen requiring reoperation and two had gas-bloat syndrome. These specific complications of the Nissen procedure were not found in the modified Toupet group.

SURGICAL TREATMENT OF long-standing gastroesophageal (GE) reflux disease has, during the last 40 years, been undertaken with a steady improvement in results.[1] Even if surgical treatment in patients with severe reflux esophagitis may be superior to medical therapy in patients who may obtain a 20% to 46% healing rate with H2-receptor blocking agents[2–6] and a high recurrence rate (more than 85%) after Omeprazole treatment,[7] the search for an operative technique with low morbidity and high healing rates continues.[2–7] This has resulted in a wide array of publications with different operative procedures. Unfortunately most of these different techniques have been presented in an uncontrolled, nonprospective fashion, whereas randomized, long-term studies are pending.

One of the most successful procedures in effectively curtailing GE reflux has been the Nissen procedure,[8] although a high morbidity rate of specific complications is related to the procedure.[9–12] The Toupet partial fundoplication, in uncontrolled studies, has been shown to offer reliable prevention of GE reflux without the specific complications related to the Nissen procedure.[13,14]

This is the background for this long-term, prospective, randomized study of the Nissen procedure *versus* the modified Toupet procedure.

Materials and Methods

Thirty-one patients without previous surgery at the GE junction about to undergo surgery for GE reflux were included and randomized into the Nissen procedure (N) or the modified Toupet procedure (T). Patient characteristics are shown in Table 1. The patients have had symptoms with or without complications of GE reflux for 12.8 ± 4.4 years (N) and 9.1 ± 2.5 years (T), respectively.

All patients were evaluated with clinical assessments, endoscopy, and esophageal manometry before operatiom and 5 years after operation, except for three patients who were evaluated at the time of reoperation after 7, 20, and 41 months, respectively. This data was included in the final assessments after 5 years.

Operative Technique

All operations were performed through an upper midline incision with division of the left triangular ligament of the liver and retraction of the liver to the right. The peritoneum and the phrenoesophageal membrane were divided just as they leave the diaphragm to the esophagus. The diaphragm surrounding the esophagus, with its left and right crus, was dissected completely free, as was the distal esophagus to a minimal length of 5 cm. The superior part of the gastrohepatic omentum, as well as the phrenogastric and superior portion of the gastrosplenic ligament,

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TABLE 1. *Patient Characteristics*

Characteristic	Nissen Group	Modified Toupet Group
Male/female	4/8	9/10
Age (years), median (range)	63 (51–78)	58 (29–75)
Length (cm), median (range)	164 (155–179)	166 (148–186)
Weight (kg), median (range)	73 (59–89)	75 (42–93)

were divided, and the esophagus was encircled with a rubber band for downward traction.

The Nissen procedure. A large stomach tube (more than 40 French) was passed down the esophagus. The anterior and posterior walls of the fundus were wrapped with the right hand to encircle the esophagus. The posterior wall was grasped and stabilized with a Babcock clamp. The posterior wall of the fundus was brought to lie beside its anterior wall counterpart at approximately the level of the GE junction. These two serosal surfaces were then sutured together (2-0 silk), including the esophagus in the stitches. Sutures were placed 1.5 cm apart resulting in a total length of approximately 4 cm. The closure was made as floppy as possible so that the index finger could pass alongside the esophagus in the wrap. No posterior plication of the diaphragmatic crura was made in accordance with the primary description of the procedure.[8]

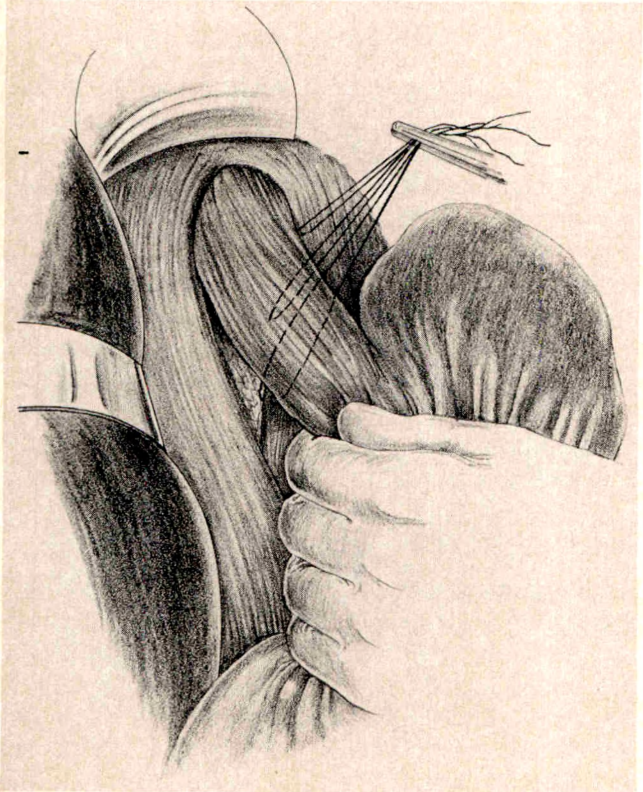

FIG. 1. Two to three nonabsorbable sutures are placed in the left crus. These are left untied with needles attached so they can be used later for fixation of the fundus to the left crus.

Modified Toupet procedure. Apart from dividing the phrenogastric and superior portion of the gastrosplenic ligament, 2 to 4 short gastric vessels were taken down to mobilize the gastric fundus. Three silk sutures were placed in the left crus and left untied for later use in fixation of the fundus (Fig. 1). The flap of the fundus was then passed behind the esophagus to the right side and held without tension with a Babcock clamp.

This portion of the fundus was then sutured to the right diaphragmatic crura with the upper suture also including the esophageal wall without penetrating the mucosa. Adapting sutures without tension were then placed between the fundoplication and the right border of the esophagus (Fig. 2). Similar attachments were made on the left side with the sutures left in place and the left diaphragmatic crura and attachment to the esophagus. The fundic portion has encircled the distal esophagus between 180 and 200 degrees (Fig. 3). This technique is a modification of the original procedure.[13,14]

The operating time and bleeding, as well as intraoperative and postoperative complications, were registered.

Clinical Assessment

The patient's symptoms (heartburn, acid regurgitation dysphagia, and retrosternal pain) were graded using a standardized questionnaire by an independent observer (TE). The following grading system was used: 0 = none, 1 = mild (easily tolerated), 2 = moderate (interfering with usual activity), or 3 = severe (incapacitating, preventing usual activity). Concomitant pulmonary symptoms were registered. In addition global assessment was made after 5 years and the outcome of surgery was graded as excellent (no residual symptoms, no medication); good (occasional

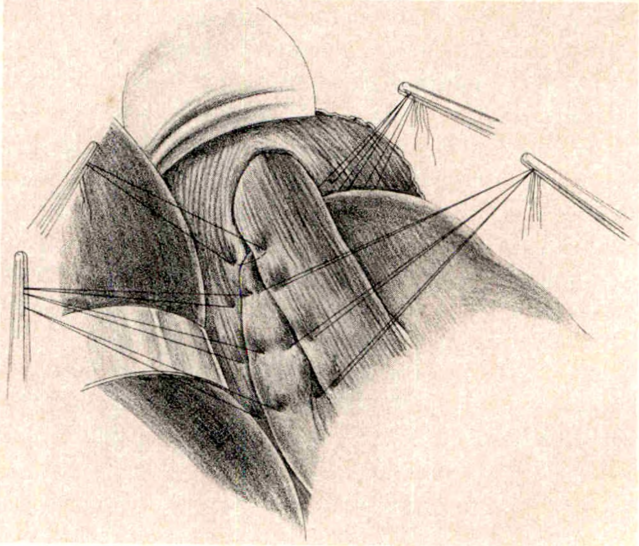

FIG. 2. Placement of suture, including upper part of the right crus, fundus, and esophageal wall.

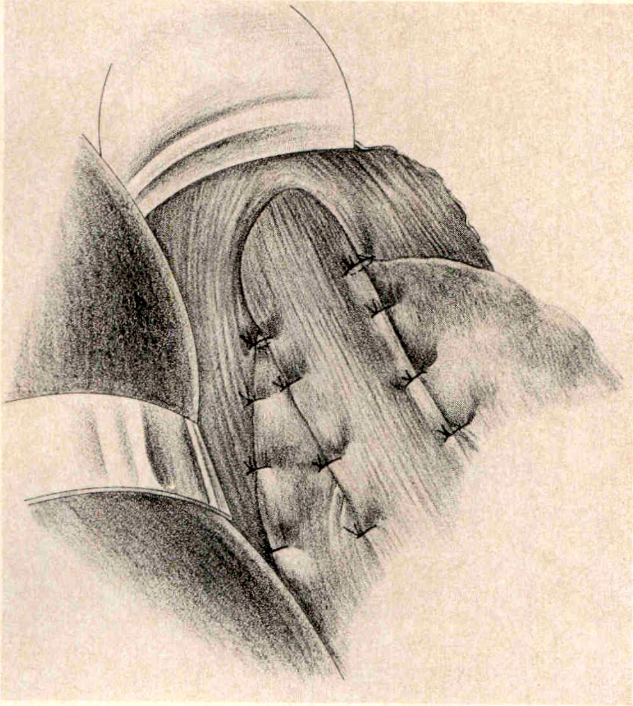

FIG. 3. Final row of sutures between the fundus and the esophagus placed in such a way that the fundus of the stomach encircles the esophagus about 250 degrees.

symptoms, no medication needed); none or only slight improvement (residual symptoms requiring medication); and worse.

Endoscopic Procedures

Esophagogastroduodenoscopy (Olympus, Axel Johnsson Instr. AB, Solna, Sweden; GIF Q10, GIF Q20, or GIF K2) was performed in a standardized manner after an overnight fast with topical anesthesia in the pharynx. The endoscopists were, at the time of endoscopy after surgery, unaware of what procedure had been carried out. The severity and extent of microscopic esophageal ulceration or erosion was scored according to a modified classification of Savary-Miller[15]: 0 = no mucosal abnormalities; 1 = superficial erosions, not confluent; 2 = superficial erosions, confluent; 3 = superficial erosions confluent around the entire circumference; 4 = peptic ulceration or stricture. If a stricture was present, dilatation was done before surgery. Biopsy specimens were taken at the site of the lesion and were equal to or more than 4 cm above the esophagogastric junction to establish whether Barrett's esophagus was present. At endoscopy the presence of hiatal hernia was noted if it was present.

Esophageal manometry. Esophageal manometry was done with intraluminal pressure measurements in a low-compliance system as previously described.[16] Esophageal motility was measured in the entire esophagus with the recording orifices 5 cm apart, and the lower esophageal sphincter (LES) pressure or the high pressure zone (HPZ) were measured with a continuous pull-through technique with the catheter withdrawn at a constant speed of 0.5 cm per minute. The lowest value of five recordings from three recording orifices at the same level was calculated. All recordings were analyzed and assessed by a single observer (KT) who was blind to what surgical procedure had been carried out.

Esophageal motility was regarded as 0 = normal peristaltic activity; 1 = peristaltic activity with less than 50% nonperistaltic contractions and dysmotility; 2 = peristaltic activity or peristalsis with more than 50% nonperistaltic contractions and dysmotility; and 3 = no peristaltic activity.

Statistical Evaluation

Values are expressed as mean ± SEM. Clinical variables were compared with Student's unpaired t test or the Mann-Whitney-Wilcoxon rank sum test.

Results

Of the 31 randomized patients, 12 had a Nissen procedure and 19 had a modified Toupet procedure. Demographic and clinical data were similar for the two groups on entry into the trial (Table 1).

There was no difference in the time required to perform the Nissen procedure (79 ± 5 minutes) *versus* the modified Toupet procedure (79 ± 8 minutes), nor was there a difference in operative bleeding (335 ± 77 mL) in the Nissen group *versus* (230 ± 49 mL) the modified Toupet procedure group. There were no deaths and the intra- and postoperative complications are shown in Table 2.

Patients undergoing the modified Toupet procedure had an excellent or good result in 95% *versus* 67% for patients undergoing the Nissen procedure (Table 3). Three patients in the Nissen group had a slipped Nissen with no improvement or worsening of these symptoms. Two patients in the Nissen group had a mild gas bloat syndrome.

The symptoms for evaluation (acid regurgitation, heartburn, retrosternal pain, and dysphagia) show there is no difference between the preoperative scoring values in the Nissen or modified Toupet procedure groups. This is exemplified by symptom scoring of acid regurgitation in Figure 4. There is an improvement in symptomatology

TABLE 2. *Complications*

Complication	Nissen	Modified Toupet
Incisional hernia	2	1
Splenectomy	1	0
Pleuritis	0	1
Wound infection	0	1
Ileus	0	1

TABLE 3. *Results More Than 5 Years After Operation*

Excellent or good results	8 (67%)*	18 (95%)
None or slight improvement	2†	1
Worse	2†	

* Two cases of "gas bloat" syndrome.
† Three "slipped" Nissens.

with both procedures, except for dysphagia both for liquids and solids in the Nissen group as exemplified by Figure 5. This is largely due to the three patients with a slipped Nissen who developed more severe dysphagia than before surgery. The three patients who were reoperated up for slipped Nissen were operated on 7, 20, and 41 months after primary surgery.

The endoscopic grading was similar in the two groups with three strictures and one Barrett's esophagus in the Nissen group and six strictures and three Barrett's esophagus in the modified Toupet group (Fig. 6). There was no difference in improvement in endoscopic grading between the two groups. One patient in the modified Toupet group was regarded as grade 4 after surgery, even though his esophagitis had disappeared because of the persistence of a long stricture. The patient has no residual symptoms of GE reflux or dysphagia.

A hiatal hernia was considered to be present in all patients in the Nissen group and in 16 of 19 in the modified

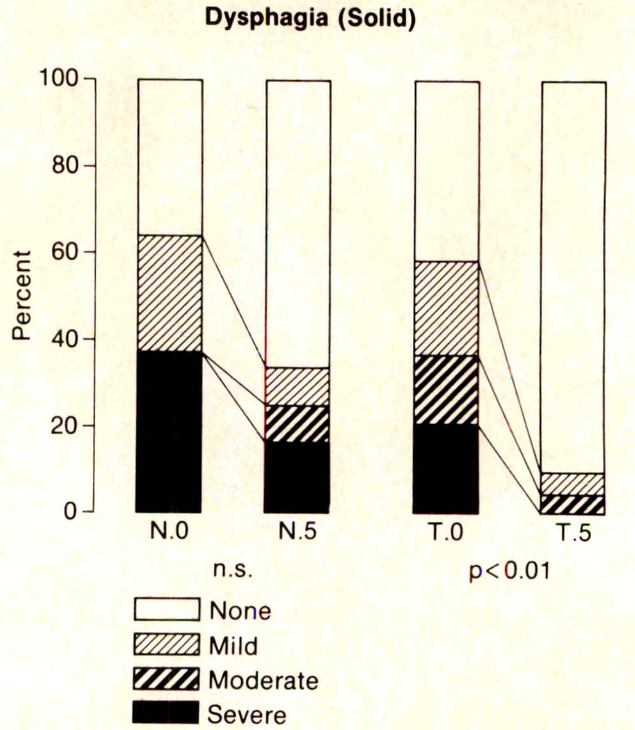

FIG. 5. Proportions of patients with no, mild, moderate, or severe dysphagia for solids before (0) or 5 years (5) after surgery with the Nissen procedure (N) or a modified Toupet procedure (T).

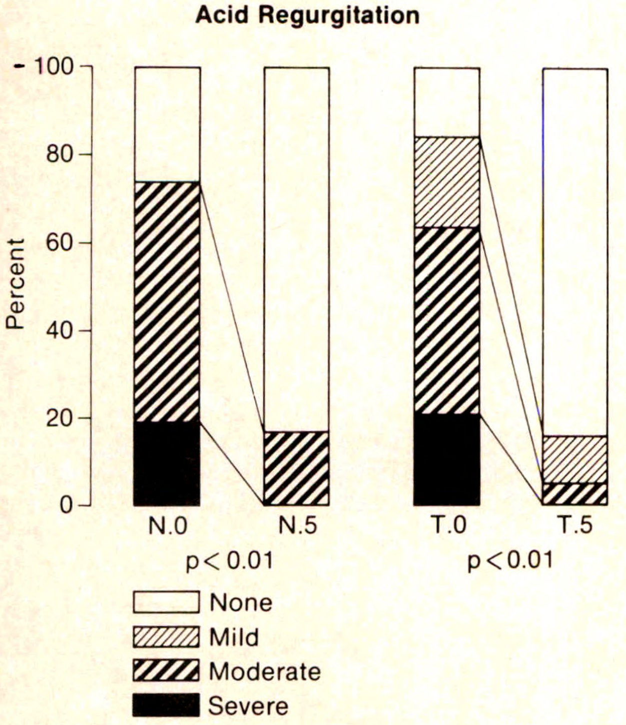

FIG. 4. Proportion of patients with no, mild, moderate, or severe acid regurgitation before (0) or 5 years (5) after surgery with the Nissen procedure (N) or a modified Toupet procedure (T).

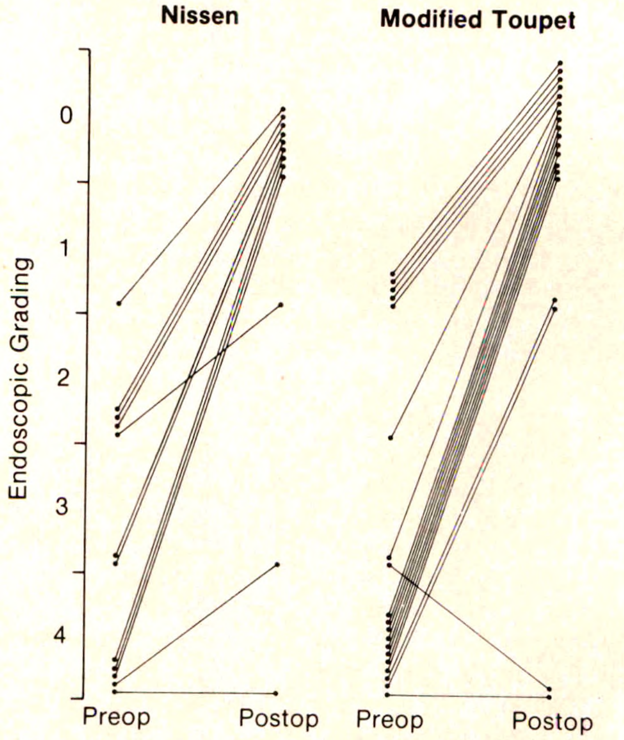

FIG. 6. Endoscopic grading of severity of esophagitis in patients undergoing the Nissen procedure and the modified Toupet procedure before and 5 years after surgery. Each line represents one patient. For comments see text.

Toupet group. Three patients in the Nissen group were considered to have a new hiatal hernia at endoscopy after surgery, which, however, turned out to be a slipped Nissen. One of the 19 patients with a modified Toupet procedure had endoscopic signs of hiatal hernia after surgery.

There was an improvement in the concomitant pulmonary symptoms as shown in Table 4.

There is no difference in the esophageal motility before or after operation between the Nissen and the modified Toupet procedures. Scoring values before and 5 years after surgery improved from 1.2 ± 0.5 to 0.3 ± 0.2 in the Nissen group and from 1.0 ± 0.5 to 0.3 ± 0.1 in the modified Toupet procedure group, although these values are not statistically significant in any of the groups.

The LES or HPZ pressure was not different in the two groups before or after surgery. The LESP increased from 5.7 ± 1.9 mm Hg to 19.5 ± 1.6 mm Hg ($p < 0.001$) in the Nissen group and from 6.7 ± 1.2 mm Hg to 16.9 ± 2.2 mm Hg ($p < 0.01$) in the modified Toupet procedure group.

Discussion

This prospective randomized long-term trial shows that patients undergoing modified Toupet procedure have excellent or good results in 95% compared to 67% of the patients undergoing the Nissen procedure. This large difference is surprising, especially because both procedures are effective in curtailing esophagitis with a 91% improvement of the endoscopic grading in the Nissen group and an 89% improvement in the modified Toupet group. The results are particularly striking in view of the fact that all the patients in the study had erosive or ulcerative esophagitis that was endoscopically extensive or severe (grades 3 or 4) in 65%.

We haven't used 24-hour pH measurements in this study because at the time this trial started (1979) it was not available in our laboratory. Both the LES and HPZ determinations are used because it is impossible after surgery to define whether the increase in LES pressure in fact is due to pressure from the fundoplication.

Both procedures are equally effective in eliminating acid regurgitation, heartburn, and retrosternal pain. However 33% of patients in the Nissen group still have dysphagia, both for solids and liquids. This is mainly due to the patients who develop one of the specific complications related to the Nissen procedure—a slipped Nissen. The slipped Nissen is the most commonly known complication in two of the largest series specifically related to complications of the Nissen repair.[9,11] Other severe complications not encountered in our series consist of fistulas such as gastrobronchial, gastrocutaneous, gastroaortic, and gastropericardial. These complications are assumed to develop from a penetrating ulcer formed in the Nissen wrap, either because of ischemia or because of hyperacidity with stasis within the wrap.[9] The importance of these complications is that they are only found after a Nissen procedure has been carried out and rarely, if ever, after other procedures. Concern about these problems with the Nissen fundoplication has produced a number of revisions in technique such as the Rosetti modification, Collis-Nissen, floppy Nissen, incomplete wraps, anchoring, and a one-stitch Nissen.[17-22] These attempts to modify the technique indicate that the original procedure is not standing the test of time.

TABLE 4. *Pulmonary Symptoms*

	Nissen		Toupet	
	Before Operation	<5 Years	Before Operation	<5 Years
Asthma	2	1	2	1
Night cough	1	0	4	1
Recurrent pneumonia	0	0	1	0

In a previous retrospective study, of 64 of our patients operated on with the Nissen repair, 89% had good or excellent results but 18% had symptoms of gas bloat syndrome, three of whom required reoperation. The gas bloat syndrome, although not life threatening, is a complication specific to the Nissen procedure that is not found after the modified Toupet procedure. In the present study, two patients had mild symptoms of gas bloat syndrome that were well tolerated compared to the symptoms before surgery.

The differences between the Nissen total fundoplication and other antireflux operations such as the modified Toupet, Hill, or Belsey Mark IV may be the difference between the nipple and the valve. Nissen fundoplication creates a nipple-like deformity that may lead to difficulties such as belching and vomiting and create the gas bloat syndrome. The other above-mentioned procedures restore, in different ways, a more valve-like mechanism that is one of the natural causes for GE competence. Even in a cadaver there is a GE gradient, which means that the stomach can be distended without reflux. This was originally described in 1878[24] and is considered to be due to a one-way flap valve at the GE junction. This concept has been partly overlooked in the literature because of the emphasis placed on the LES. This doesn't mean that the LES is unimportant, but rather that the GE competence also requires a posterior attachment of the GE junction so that the esophagus enters the stomach in an oblique fashion, thereby creating a flap-valve mechanism. We believe that these principles are obtained and exaggerated with the modified Toupet procedure. The GE flap valve becomes tightly opposed to the lesser curve aspect of the GE junction when intragastric pressure is increased, thereby preventing reflux.[25]

This is a small randomized trial but with a long-term follow-up. We decided not to continue this study further because the differences were prominently in favor of the modified Toupet procedure. For this one may be criticized, but because two of the slipped Nissens occurred during the first 2 years when the study was still in progress, we believed it was difficult, as surgeons, to continue to include patients when we would clearly be biased in favor of the modified Toupet procedure. However it should be noted that despite the small number of patients, a significant difference in the outcome after 5 years exists. We have, after the termination of this study, performed more than 300 modified Toupet procedures with a cumulative recurrence rate of less than 5% and no deaths, with a median follow-up time of 3.5 years (range, 0.4 to 7 years).

In conclusion this prospective randomized trial shows that the Nissen procedure and the modified Toupet procedure are effective in curtailing symptoms of GE reflux, except that the Nissen procedure, in our hands, has unacceptable complications specific to the procedure.

Acknowledgments

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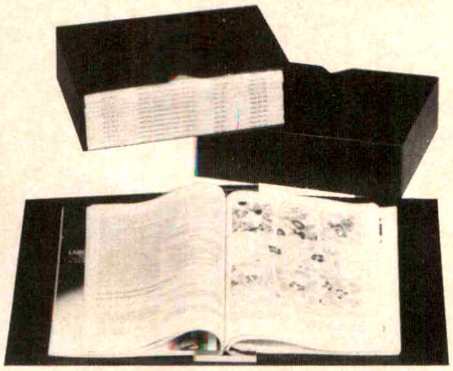

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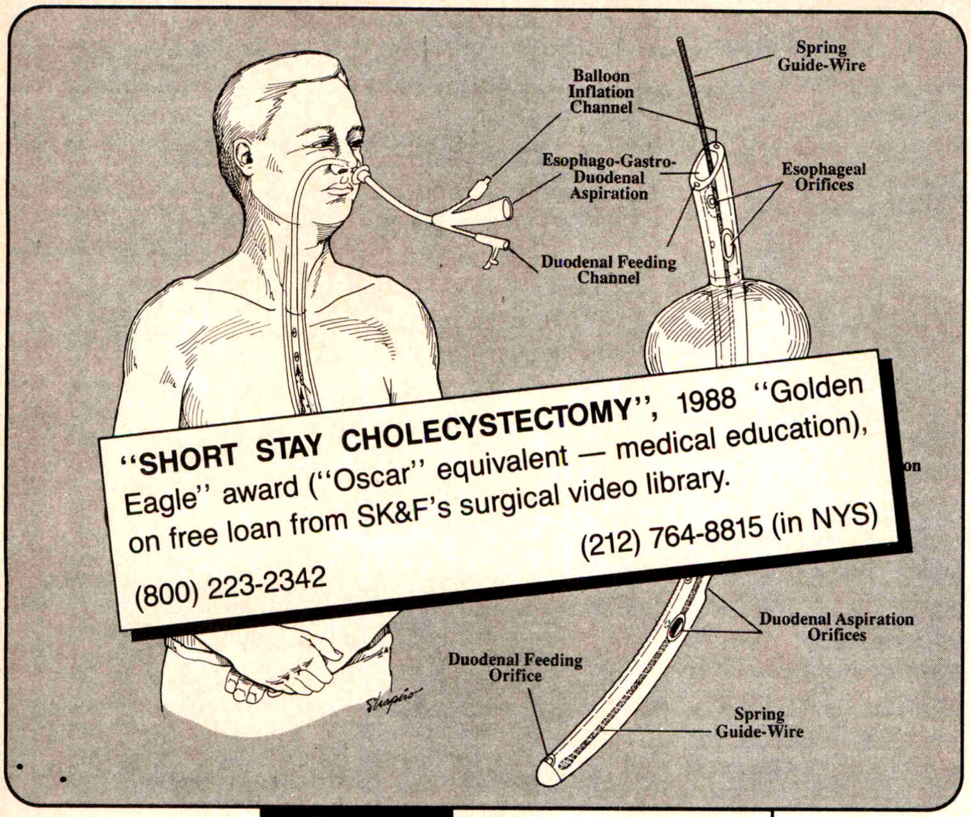

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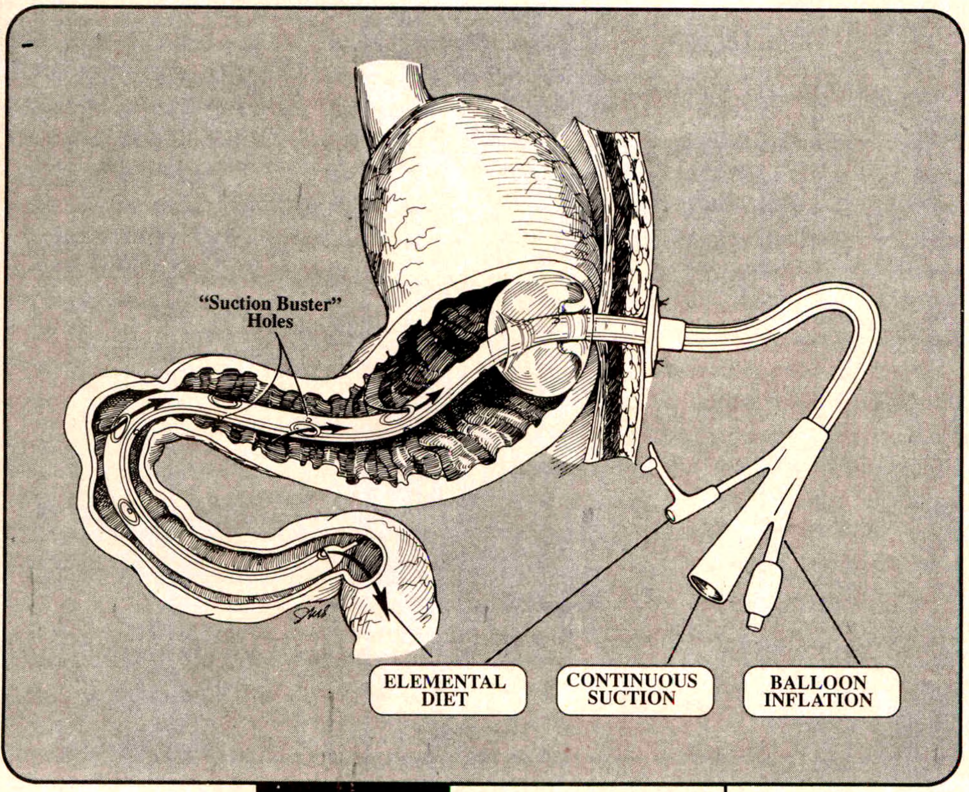

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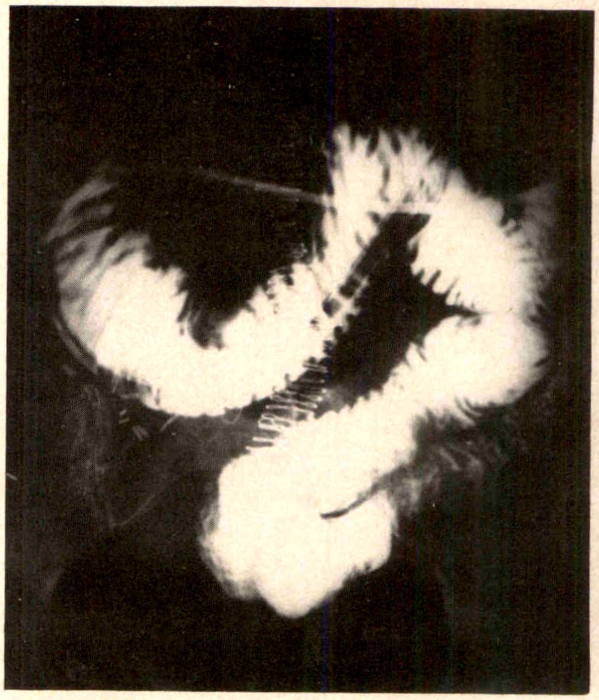
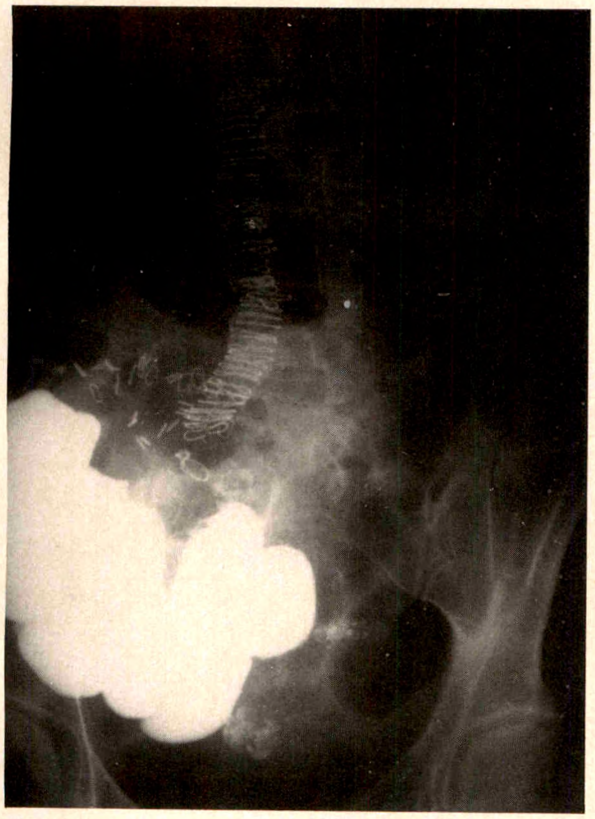
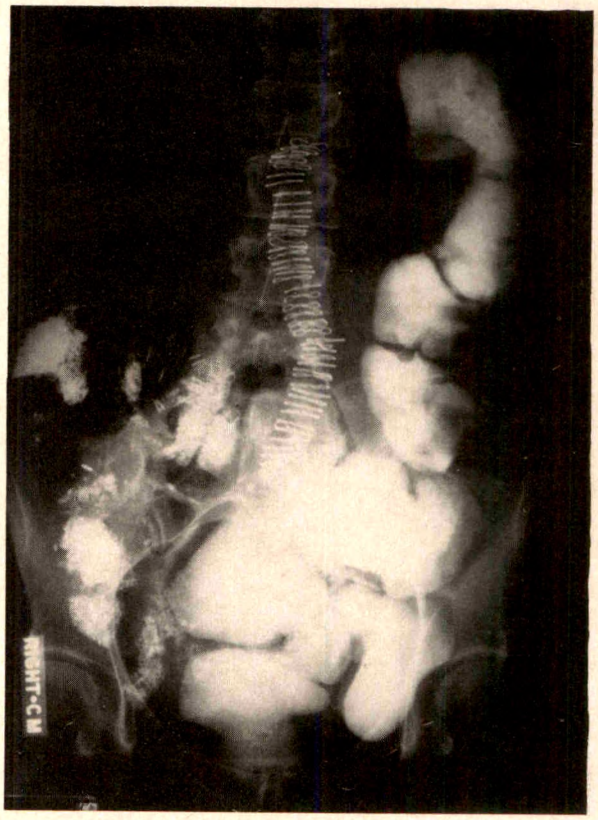


A. Study @ 5 minutes (5 hours postop). Note efficient removal of all excess barium, with none reaching the stomach.



B. Motility @ 4 hours (9 hours postop). All barium is within the ileum.



C. Motility @ 16 hours (21 hours postop). Barium is exiting in a spontaneous bowel movement.

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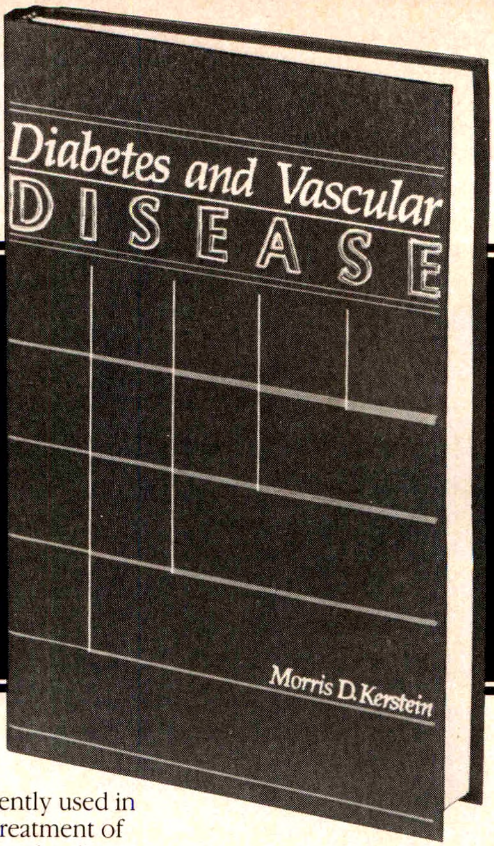

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Long-Term Injection Sclerotherapy Treatment for Esophageal Varices

A 10-Year Prospective Evaluation

JOHN TERBLANCHE, CH.M., F.C.S.(SA), F.R.C.S.(Eng), F.R.C.P.S.(Glasg), F.A.C.S.(Hon),
DELAWIR KAHN, CH.M., F.C.S.(SA), and PHILLIPUS C. BORNMAN, M.Med.(Surg), F.R.C.S.(Edin)

Long-term injection sclerotherapy after proved variceal bleeding was assessed in 245 patients. The majority had alcoholic cirrhosis and the patients were equally distributed between modified Pugh-Child's risk grades A, B, and C. Esophageal varices were eradicated in 88% of the 140 patients who survived long enough for analysis, and remained eradicated for a mean of 19.4 months. The incidence of recurrent variceal bleeding after the first hospital admission was 0.02 bleeding episodes per patient month of follow-up study and was markedly reduced after eradication of varices. The overall cumulative survival rates at 1, 5, and 10 years were 54%, 39%, and 29%, respectively. The prognosis was influenced by the risk grade and the number of variceal bleeds before entering the study and to a lesser extent by the etiology of the cirrhosis. Fifty-two per cent of the patients died during the 10-year period. Liver failure was the major cause of death. Complications were mostly of a minor nature but they became cumulative with time. Minor complications included mucosal slough and injection-site leak, although the latter had an associated mortality risk. Significant esophageal stenosis and esophageal rupture were rare. As a result of this study a more radical surgical policy is proposed for sclerotherapy failures. These are defined as patients in whom varices are difficult to eradicate or who continue to have major variceal bleeds. Such patients should be subjected to either a portosystemic shunt or a devascularization and transection procedure.

From the Department of Surgery, Surgical Gastroenterology, and the Medical Research Council Liver Research Center, the University of Cape Town, and Groote Schuur Hospital, Cape Town, South Africa

ALTHOUGH INTRODUCED IN 1939 by Crafoord and Frenckner, injection sclerotherapy has only recently become established as the recommended treatment of choice in the management of patients with acute esophageal variceal bleeding.[1-4] This is supported by the data from the three completed controlled trials.[5-7] On the other hand, its role in the long-term management of patients after an esophageal variceal bleed remains controversial.[8] Studies have shown that repeated sclerotherapy eradicates esophageal varices in the majority of patients, and that once the varices have been eradicated, recurrent variceal bleeding is virtually eliminated.[1,8-13] However controlled trials to assess the effect of sclerotherapy on survival have produced conflicting results.[9-13] Follow-up in most previous reports has been short. This paper reviews the prospectively documented results from a 10-year analysis of injection sclerotherapy in the long-term management of patients after variceal bleeding.

Patients and Methods

All patients admitted to the adult wards of Groote Schuur Hospital during the 10-year period between August 1975 and August 1985 were assessed. Patients had to have proved esophageal variceal bleeding diagnosed by fiberoptic endoscopy within 24 hours of hospital admission for massive upper gastrointestinal hemorrhage to be included in the study. Thus all patients included were either referred at the time of active variceal bleeding or after a proved variceal bleed. All injection treatments, both emergency and elective, were analysed in these patients to assess the role of sclerotherapy in long-term management. All patients were studied prospectively and the data was collected on computer pro forma sheets. Those patients included in randomized studies gave informed consent, and each study was approved by the Faculty of Medicine Ethics and Research Committee.

During the 10-year study period, 304 patients satisfied the inclusion criteria. With the exception of two patients who were not referred by the physician in charge early in the study, this represents our complete experience of

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This study was supported by the South African Medical Research Council and the Staff Research Fund of the University of Cape Town.

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treating adult patients with proved bleeding esophageal varices since the introduction of sclerotherapy. A total of 245 of these 304 patients were ultimately analyzed. The 59 exclusions included the 35 control patients in a previous randomized trial[9] and 24 patients with inadequate follow-up data. The 35 trial patients were excluded because they did not receive repeated sclerotherapy treatments in long-term management, although emergency sclerotherapy was used when required to control acute variceal bleeds.[9] The remaining 24 patients were excluded because of incomplete follow-up data. Only one local patient refused to comply with regular follow-up. Eleven patients moved abroad and 12 patients lived at great distances from our center. The mean available follow-up period of these excluded patients was 7.9 ± 2.1 months (range, 0.2 to 35 months).

The 245 patients analyzed in this study consisted of 169 males and 76 females with a mean age of 46.06 ± 1.14 years. The etiology of the portal hypertension is shown in Table 1. The majority had cirrhosis (73%), with alcohol acting as the etiologic agent in 139 patients. Cryptogenic cirrhosis and portal vein thrombosis were the other main causes. Our modified numerical Pugh-Child's risk grade was used to assess the severity of the liver disease.[14] Seventy-two patients were Grade A, 81 were Grade B, and 78 were Grade C when assessed on first admission to our hospital. Fourteen patients were not classified.

Three techniques of injection sclerotherapy were used during the 10-year study period. Initially injections were carried out under general anesthesia with the rigid 50-cm esophagoscope, modified with a slot, and the sclerosant, ethanolamine oleate, injected directly into the varix. The anesthesia and injection techniques have been described in detail.[2,14,15] Since 1981 sclerotherapy was also performed with the fiberoptic endoscope under sedation with diazepam or pethidine or both. The sclerosant, ethanolamine oleate, was injected by a combined technique both into the variceal channels and submucosally, with a total of between 5 and 20 mL of sclerosant injected on any one occasion.[15] The flexible scope technique was used exclusively after completing a controlled trial comparing it with the rigid endoscope in July 1984.[16] In 1983 for approximately 4 months a small group of patients were injected with the fiberoptic endoscope using the paravariceal technique described by Paquet[1] with polidocanol (aethoxysclerol) as the sclerosing agent.

Repeat injection sclerotherapy was performed whenever residual varices were demonstrated by fiberoptic endoscopy. In the first 25 months sclerotherapy was undertaken at 1 week and then at 1 month and thereafter every 3 months until the varices were eradicated. The preliminary analysis identified a group of patients whose varices proved difficult to eradicate,[14] and subsequently a policy of assessing and injecting varices at weekly intervals was adopted, although not always rigidly maintained.

TABLE 1. *Etiology of Portal Hypertension*

Diagnosis	Number	Percentage	
Alcoholic cirrhosis	139	57	73
Cryptogenic cirrhosis	40	16	
Chronic active hepatitis	7	3	
Portal vein thrombosis	40	16	
Other	8	3	
Undiagnosed	11	4.5	

The treatment of the initial and subsequent acute variceal bleeding episodes has been described elsewhere.[2,17] Patients with variceal bleeding that had stopped spontaneously by the time of emergency endoscopy had no further specific emergency therapy, whereas patients who were actively bleeding from varices at the time of endoscopy were treated with Sengstaken balloon tube tamponade and subsequent early emergency injection sclerotherapy.

The effect of the etiology of the liver disease, the modified Pugh-Child's risk grading, and the number of previous variceal bleeds on survival were determined using the univariate analysis of survival according to the Kaplan–Meier method. The Wilcoxon test was used to assess significance.

Results

Eradication of Varices

Eradication and recurrence of esophageal varices after sclerotherapy was assessed in 140 of the 245 patients. One hundred five patients died within 3 months of entering the study. This arbitrary time was considered too short to assess eradication of varices and these patients were therefore excluded from this particular aspect of the analysis.

Esophageal varices were eradicated in 123 of the 140 patients (88%). A median number of five injections (range, 1 to 16 injections) during a mean of 9.25 ± 0.85 months (range, 0.5 to 60 months) were required to eradicate the esophageal varices. Esophageal varices remained eradicated for a mean of 19.4 ± 1.65 months (range, 0.3 to 100 months). Varices recurred in 37 patients after a mean of 15.7 ± 1.7 months (range, 2 to 48 months). Of the patients whose varices did not recur, 13 died with their varices eradicated after a mean of 16.9 ± 4.6 months (range, 1 to 48 months), and 73 patients were alive at the end of the study with a clear esophagus after a mean of 21.6 ± 2.5 months (range, 1 to 100 months) after eradication.

The 17 patients whose varices were not eradicated received a median number of five injections during a mean 10.4 ± 1.18 months. The varices were reduced in size but were not eradicated.

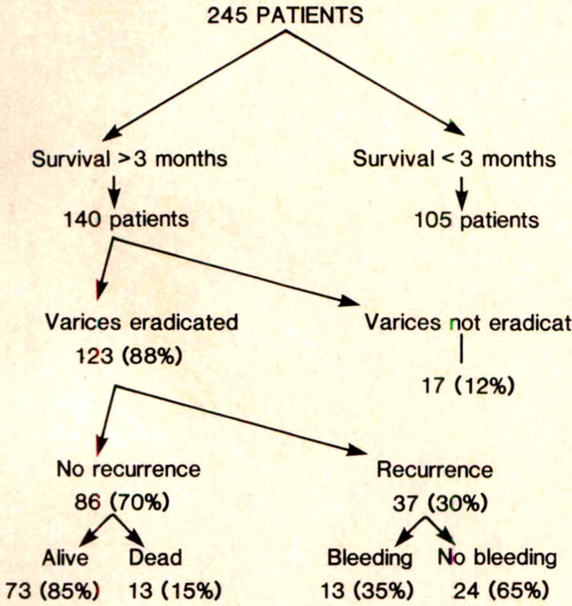

FIG. 1. Eradication and recurrence of esophageal varices.

Varices were eradicated in 39 of the 40 patients, with extrahepatic portal venous obstruction after a median number of six injections during a mean of 11.08 ± 1.68 months. However in only 50 of the 67 patients (75%) with alcoholic cirrhosis who survived for more than 3 months were varices eradicated. Thus a median number of six injections during a mean of 8.76 ± 1.47 months were needed. Of the 30 nonalcoholic cirrhotic patients who survived for more than 3 months, varices were eradicated in 21 (70%) after five injections during 8.05 ± 1.11 months.

Thirteen of the 37 patients with recurrence of esophageal varices after eradication presented with variceal bleeding; this occurred after a mean of 15.5 ± 3.8 months. Some had missed follow-up appointments. When varices recurred they were usually small and easily re-eradicated by sclerotherapy.

Recurrent Variceal Bleeding

Recurrent variceal bleeding was defined as an endoscopically proved variceal bleed requiring transfusion. In this study the incidence of variceal bleeding was assessed after the first admission in the total group of 245 patients treated with repeated sclerotherapy. Forty-one patients (17%) had a total of 119 variceal bleeds during 81 subsequent admissions. The number of rebleeds from esophageal varices was 0.02 per patient month of follow-up study. Fifty-six of the bleeding episodes settled with conservative treatment that included blood transfusions and intravenous vasopressin. The remaining 63 variceal bleeds (53%) were treated with esophageal balloon tamponade followed by emergency injection sclerotherapy.

Recurrent variceal bleeding was unusual after the varices had been eradicated and occurred in only 13 of the 123 patients (10.6%). Looked at differently, further variceal bleeding was frequent in the subset of patients who developed recurrent varices (13 of 37 patients: 35%; Fig. 1).

Esophageal Complications (Table 2)

During the study period the 245 patients under consideration received a total of 1207 emergency and elective sclerotherapy treatments. This resulted in a total of 287 esophageal complications in 135 patients. Thus 55% of patients had one or more complications and one in four sclerotherapy treatments was followed by a complication.

Mucosal slough or local ulceration at the injection site was presumably produced by the sclerosant and was found at follow-up endoscopy on 235 occasions in 114 patients. Although some patients had subsequent sclerotherapy delayed because of the mucosal slough, it rarely led to any serious problems.

An injection site leak, a term used by our group for a contained local leak,[2,17,18] was suspected in patients with persistent pain and pyrexia after sclerotherapy. The diagnosis was confirmed by demonstrating a localized leak on barium or gastrografin swallow. This complication occurred on 17 occasions in 17 patients and was treated with antibiotics and intravenous fluids with no oral feeding or with fine-bore silastic nasogastric tube feeding. Although the leak settled on conservative treatment, repeat sclerotherapy was delayed and this was partly responsible

TABLE 2. *Complications in 245 Patients (1207 Sclerotherapy Treatments)*

Complication	Complications per Sclerotherapy Treatment: Number of Complications	Complications per Sclerotherapy Treatment: Percentage	Complications per Patient: Number of Patients with Complications	Complications per Patient: Percentage
Mucosal slough	235	19.5	114	46.5
Injection-site leak	17	1.4	17	7
Stenosis	31	2.6	31	13
Esophageal rupture	4	0.3	4	1.6
Total complications	287	24	135	55

for a few patient deaths due to repeat bleeding and subsequent liver failure.[18]

Esophageal stenosis was found on barium swallow on 31 occasions in 31 patients who complained of persistent dysphagia after sclerotherapy. It was usually a transient phenomenon, but five patients required esophageal dilatation for relief of symptoms. Three patients were dilated more than five times and two of these three patients still had minimal dysphagia 12 months after the initial complication. The remaining patients were symptom free.

The most serious complication, rupture of the esophagus, occurred in four patients who were injected electively using the rigid esophagoscope. The cervical esophagus was ruptured in two patients, and the lower esophagus in the other two patients. Three patients were treated surgically. Two of the four patients died, including the patient treated conservatively who died of liver failure.

Survival Analysis

The cumulative survival for the total group of 245 patients, calculated by means of life table analysis, is shown in Figure 2. The probability of surviving 1 month was 72% and the 1-year survival rate was 54%. The cumulative survival rate was 39% at 5 years and 29% at 10 years.

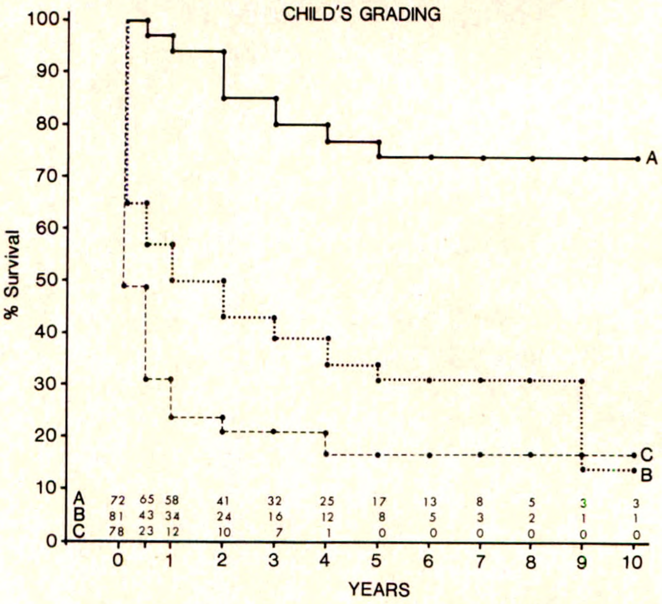

FIG. 3. Cumulative survival rates by life table analysis for patients at Child's risk grades A, B, and C. The numbers above the abscissa denote the number of patients at risk of dying during the observation period in each group.

The effect of the initial admission modified Pugh-Child's grading on survival is shown in Figure 3. The survival for patients who were grade A was significantly better than for those who were grade B ($p<0.0001$) and the survival for patients who were grade B was significantly better than those who were grade C ($p<0.005$). As expected patients with extraheptatic portal venous obstruction (Fig. 4) fared significantly better than the patients with cirrhosis ($p<0.0001$). The effect on survival of the etiology of the cirrhosis (alcoholic *vs.* nonalcoholic) just reached significance ($p<0.05$). Patients who presented with their first variceal bleed (Fig. 5) had a significantly poorer survival rate than did those with between one and three previous variceal bleeds ($p<0.005$), and the latter group of patients

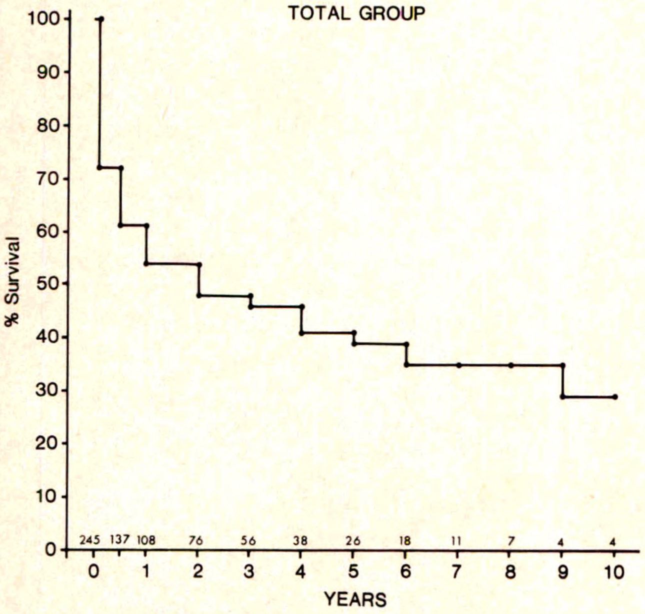

FIG. 2. Cumulative survival rates by life table analysis for all patients. The numbers above the abscissa denote the number of patients at risk of dying during the observation period in each group.

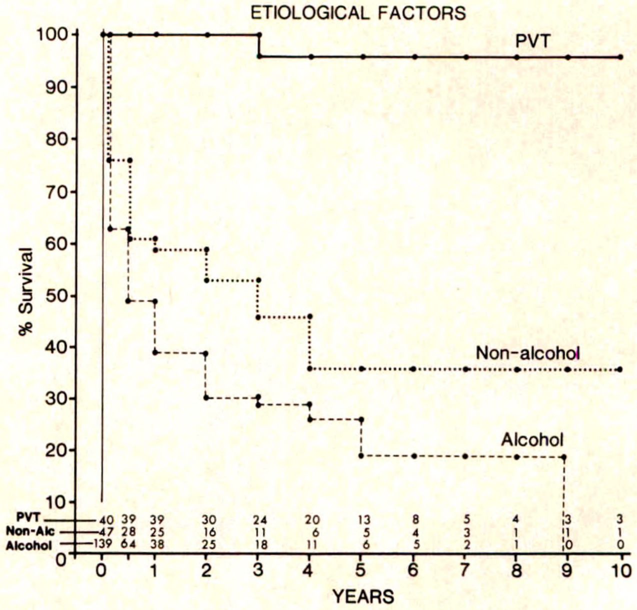

FIG. 4. Cumulative survival rates by life table analysis for alcoholic and nonalcoholic cirrhotic patients and patients with portal vein thrombosis. The numbers above the abscissa denote the number of patients at risk of dying during the observation period in each group.

had a significantly poorer survival rate than did those patients with many previous variceal bleeds ($p<0.005$).

Causes of Death (Table 3)

One hundred twenty-eight (52%) of the 245 patients died during the course of the 10-year study period. The cause of death was often multifactorial and was sometimes difficult to define, particularly the role of variceal bleeds in precipitating liver failure. Liver failure was the major cause of death: it was the primary cause of death in 72 patients and was associated with multiple organ failure in 34 patients. Eight of the 12 cardiorespiratory deaths were due to aspiration pneumonia or pulmonary embolus. Of the 8 patients who died primarily from bleeding, 4 died at home, 1 had a disseminated intravascular coagulopathy, and 1 died with a Sengstaken tube *in situ.*

Discussion

The controversy surrounding the ideal long-term management policy for patients who have bled from esophageal varices remains unresolved.[8] The place of long-term pharmacologic therapy with beta blockade remains highly controversial.[19–21] We believe that pharmacologic therapy should be restricted to controlled trials or major institutions. The surgical options, including portosystemic shunts and devascularization and transection operations, are major procedures that have significant attendant morbidity and mortality risks. Injection sclerotherapy has several presumed advantages. It is easy to perform and is associated with low initial morbidity and mortality rates. Furthermore liver function is not affected and the incidence of encephalopathy is not increased. However varices may be difficult to eradicate in some patients and they do recur and bleed after eradication. Patients also require follow-up for life with repeated fiberoptic endoscopy to assess and treat recurrent varices when they occur.[8] Complications also become cumulative with time, although serious complications are infrequent.[18]

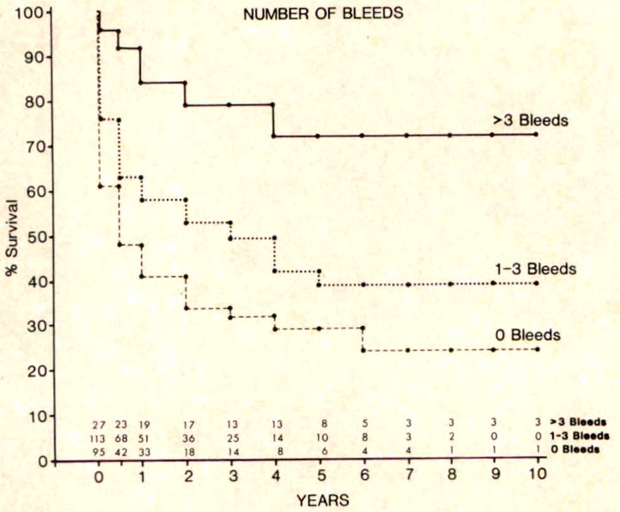

FIG. 5. Cumulative survival rates by life table analysis related to the number of variceal bleeds before entering the study. The numbers above the abscissa denote the number of patients in whom the data was available who were at risk of dying during the observation period in each group.

TABLE 3. *Causes of Death*

Cause of Death	Number
Liver Failure	
Primary	72
Associated multiple-organ failure	34
Cardiorespiratory	12
Bleeding	8
Sepsis	2
Total	128

Recent studies have emphasized the value of injection sclerotherapy in the management of patients with esophageal varices.[1–14] It is widely held to be the treatment of choice for acute variceal bleeding, with bleeding control rates in excess of 90%.[1–7] Its efficacy in controlling acute variceal bleeding and its ready availability and simplicity has probably led to its current widespread use in the long-term management of patients after variceal bleeding. Here repeated injection sclerotherapy has been shown to eradicate esophageal varices in the majority of patients, and once varices were eradicated, recurrent variceal bleeding was virtually eliminated when follow-up was adequate. However the effect of repeated sclerotherapy on long-term survival remains unresolved. Controlled trials have produced conflicting results.[8,22] The King's College Hospital trial showed a highly significant improvement in survival with sclerotherapy,[11] whereas the trials from Copenhagen[10] and Los Angeles[12] failed to show a clear difference, and the studies from Cape Town[9] and Stockholm[13] showed no improved survival. The differences between the trials have been discussed previously.[8,9,22] Warren et al.'s[23] controlled trial comparing repeated sclerotherapy with the distal splenorenal shunt concluded that, although endoscopic sclerosis had a higher rate of rebleeding, it resulted in significantly improved survival when backed by shunting for those patients who were considered to be failures of sclerotherapy. This supports the use of sclerotherapy as the initial modality of treatment. Unfortunately two other controlled trials have failed to confirm an advantage for sclerotherapy when compared with distal splenorenal shunts,[24,25] but neither is truly comparable with the trial of Warren's group.

Previous studies of repeated sclerotherapy have been hampered by small numbers of patients and limited follow-up. The present evaluation of injection sclerotherapy conducted prospectively during a 10-year period included 245 patients and represents the total experience of a single center. All patients had either suffered previous endoscopically proved variceal hemorrhage or were referred specifically with an acute variceal bleed. This study confirms that repeated sclerotherapy can successfully obliterate gross esophageal varices in the majority of patients. Most patients require repeated injections to eradicate varices. Although the median number of sclerotherapy treatments was five, sometimes a single injection was sufficient, while other patients required up to 16 treatments. Overall the varices remained eradicated for an average of 19.4 months. However in 13 patients, variceal bleeding due to recurrent varices occurred at a mean of 15.5 months after eradication. Thus once varices are eradicated we advocate that the first follow-up endoscopy should be performed at 3 months to confirm eradication and then every 6 to 12 months to diagnose and treat recurrences early before their rebleeding.

When recurrent esophageal varices occur they are usually small and easily re-eradicated with one or two injections. Although it took slightly longer with a similar number of injections, esophageal varices were more frequently successfully eradicated in patients with extrahepatic portal vein obstruction than in those with cirrhosis. Esophageal varices proved difficult to eradicate in 12% of the patients evaluated. These 17 patients had persistent varices, despite a median number of five injections during an average of 10.4 months. Why varices in some patients are difficult to eradicate is unclear. We have also not rigidly adhered to our policy of repeated weekly injections until eradication, as evidenced by the many months it took to eradicate varices in some patients. In light of this we advocate regular weekly endoscopy and sclerotherapy. We have also realized that more major surgery may be indicated earlier for patients in whom sclerotherapy fails. Our group has persisted too long with sclerotherapy in patients with varices that are difficult to eradicate and in patients with troublesome recurrent variceal bleeding. As a result of this 10-year study, we recommend that such patients be classified as failures of sclerotherapy and be evaluated early for a shunt or a devascularization and transection operation. Although controlled trial data is lacking, support for this policy is provided by the Emory trial[23] in which combining distal splenoral shunt with sclerotherapy in sclerotherapy failures resulted in improved survival when compared with shunts alone. Cello et al.[26] have reached a similar conclusion after long-term follow-up of their trial patients in whom emergency portacaval shunting was compared with sclerotherapy in poor-risk alcoholic patients.

The risk of recurrent variceal bleeding in the present study (0.02 bleeds per patient per month at risk) compares favourably with reports in the literature.[14,27] Only 13 of 123 patients (10.6%) had further variceal bleeding after eradication of varices, but this constituted 35% of the patients with recurrent varices (Fig. 1). Our follow-up was not rigorous enough because a number of these patients missed a planned visit and endoscopy. Rigorous follow-up is essential. Nearly one half of the recurrent variceal bleeds were of a minor nature and settled on conservative therapy, which included blood transfusion in all and a vasopressin infusion in some patients. The remaining 53% required initial balloon tamponade followed by acute injection sclerotherapy to control life-threatening recurrent bleeds.

A detailed analysis of the complications in the total group of 304 patients is presented elsewhere.[18] The present study evaluated the complications occurring in the 245 patients included in the long-term study and reviewed the combined complications due to both emergency and elective sclerotherapy treatment in these patients. Complications were frequent, occurring after one in four sclerotherapy treatments and in more than one half the patients, but were mostly of a minor nature.[18] Asymptomatic esophageal slough or ulceration at the injection site was the most common complication and was detected at the follow-up endoscopy. It was usually of little significance in the overall management of the patient, but occasionally subsequent sclerotherapy had to be delayed. It has even been suggested that such ulceration, when it is produced after the varices have been thrombosed, is followed by re-epithelialization and better sclerotherapy control of recurrent bleeds.[28] Injection site leaks, as defined by our group,[2,17,18] occurred in 17 patients and were successfully treated with conservative measures, although subsequent sclerotherapy was delayed and some patients died of liver failure. Other serious complications included esophageal stenosis and rupture. Esophageal stenosis was significant in only 5 of the 31 patients with this complication and all responded to bougienage, although two had residual minimal dysphagia at 1 year. Rupture of the esophagus was confined to the use of the rigid esophagoscope in the elective setting and occurred after four of the total of 1207 injection sessions. In two patients with marked osteoarthritis of the cervical spine, the cervical esophagus was ruptured. The mortality rate after esophageal rupture was 50%. Although many of the complications were minor, the cumulative complications with time made them a problem for some patients.

Although a survival advantage after repeated sclerotherapy remains in doubt,[8] our 10-year evaluation has produced some interesting findings. Adult patients with extrahepatic portal vein obstruction have an excellent prognosis and varices can invariably be eradicated. We have concluded that repeated sclerotherapy is the treatment of choice in such patients.[29] Liver failure was the major cause of death in cirrhotic patients and was largely related to the underlying liver pathology. However the role of variceal bleeding, particularly repeated bleeds, and associated shock in precipitating or aggravating liver failure is difficult to quantitate. As expected the survival in patients who were Child's grade A was significantly better than in patients who were grades B or C. The etiology of the cirrhosis had some influence on survival. However patients with many variceal bleeds before entering the study had a significantly better chance of survival than did patients presenting with first bleeds. Perhaps this novel finding should not have come as a surprise. The reason is not known but it could be because such patients are more likely to live after having survived previous bleeds.

The present study has confirmed our earlier finding that repeated sclerotherapy successfully eradicates esophageal varices in most patients.[9] Eradication has proved most successful in patients with extrahepatic portal vein obstruction. Complications, although usually minor, are frequent and cumulative with time and do pose a problem. There is an acceptably low incidence of recurrent variceal bleeding after the first hospital admission, but when it does occur more than 50% are major life-threatening bleeds. As a result of this study the following policy is advocated. When varices are diagnosed, endoscopy and sclerotherapy should be performed at least at weekly intervals until all varices have been eradicated, unless sclerotherapy is prevented by local slough or ulceration. Thereafter the next repeat endoscopy should be at 3 months to confirm variceal eradication. Subsequently endoscopy should be performed at 6-to-12 month intervals to diagnose recurrent varices early. Recurrent varices should be similarly treated with at least weekly sclerotherapy treatments until eradicated. A more radical approach to sclerotherapy failure is proposed. We now define failures as patients in whom varices are difficult to eradicate using a weekly injection schedule or in whom significant variceal bleeding continues during the course of treatment. We recommend more major surgery earlier in such patients, either a shunt or a transection and devascularization operation. The studies of portosystemic shunts by Warren et al.[23] and Cello et al.[26] provide support for such a policy. New controlled trials are required to confirm whether this policy will improve overall survival.

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Early Diagnosis of Esophageal Cancer

Analysis of 11 Cases of Esophageal Mucosal Cancer

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We reviewed 11 patients with esophageal mucosal carcinoma in various aspects to improve the early diagnosis of the disease. Eighteen lesions measuring 0.5 to 5.0 cm were confirmed histologically in the 11 cases. Histologically 10 of the 18 lesions were carcinomas *in situ* (ep cancer), and the other 8 lesions were carcinomas confined to the mucosa other than ep cancer (mm cancer); all 18 lesions were squamous cell carcinomas. Six (85.7%) of the seven mm cancers showed abnormal radiographic findings regardless of the size. Similarly these findings were noted on four of five (80%) ep carcinomas 2 cm or larger in size. All 15 lesions diagnosed before operation showed abnormal findings on conventional endoscopy regardless of the size and depth of transmural invasion. Morphologic change was observed in 9 lesions (53.3%), while 13 (86.7%) showed color change; most of the lesions (80%) were manifested as redness. Dyeing of the resected specimen with Lugol solution (Katayama Chemical Industries, Osaka, Japan) showed all 18 cancerous lesions as unstained areas. Among the 18 lesions, two lesions were unstained areas, which agreed with the areas determined histologically. An additional lesion was visible with dye endoscopy as an unstained area but it was not visible with radiography or conventional endoscopy. Dye endoscopy using Lugol solution is very important because it allows detection and evaluation of the extent of esophageal mucosal cancer.

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RECENTLY THERE APPEARED several reports[1–4] describing early stages of cancer in the esophagus, with marked advances in radiologic and endoscopic diagnosis in the diseases of the alimentary tract. The Japanese Society for Esophageal Diseases[5] defines superficial esophageal cancer as tumors whose transmural invasion is confined to the submucosa. This society also defines early esophageal cancer as superficial cancers free of lymphatic metastasis. Furthermore lesions confined to the esophageal mucosa are called mucosal cancers. Among these are those confined to the epithelial layer, the ep cancer, and those whose transmural invasion is the lamina propria mucosae or the muscularis mucosae, the mm cancer.[5] Unlike early gastric cancer, superficial esophageal cancers associated with lymphatic metastasis and those whose transmural invasion is up to the submucosa show much worse prognosis than ep and mm cancers. Based on this fact, in recent trends, esophageal mucosal cancers are treated as early ones. In detecting superficial esophgeal cancer, dye endoscopy by Lugol solution (Wisconsin Pharmacal Co., Jackson, WI) plays an important role because of the minimal morphologic change of the cancer.[6]

In this study, we reviewed 11 patients with esophageal mucosal carcinoma who were recently operated on to elucidate key points in the early diagnosis.

Patients and Methods

The 11 patients included in this study were operated on at Kumamoto University Medical School, Kumamoto Regional Medical Center, Kumamoto Municipal Hospital, or Kumamoto Red Cross Hospital. There were ten men and one woman and their ages ranged from 46 through 77 years, with an average age of 64.2 ± 8.7 years (Table 1). Multiple cancers were detected in four patients (patients 2, 4, 5, and 6). Patient 2 had 4 lesions; patient 4, 3 lesions; and patients 5 and 6, 2 lesions each (11 lesions in all). Histologically 10 of the 18 lesions were carcinomas *in situ*, and the other 8 lesions were mucosal carcinoma; all 18 lesions were squamous-cell carcinomas.

All the patients received radiography, conventional endoscopy, and biopsy. Dye endoscopy[7] by Lugol solution

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TABLE 1. *Clinical Data and Pathohistology of the Lesion in 11 Patients with Esophageal Mucosal Cancer*

Patient	Lesion	Sex	Age (yrs)	Symptoms	Coexistent Digestive Disease	Opportunity of Detection	Location	Gross Type	Depth of Cancer	Histologic Type
1	1	M	67	none	none	medical check-up	lower	flat	ep	mod SCC
2	2A	F	58	smart	none	symptoms	upper	flat	ep	mod SCC
	2B						upper	flat	ep	mod SCC
	2C						upper	flat	ep	mod SCC
	2D						middle	flat	mm	mod SCC
3	3	M	68	SGC	GC	other disease	middle	flat	ep	mod SCC
4	4A	M	67	none	GC	other disease	upper	flat	ep	mod SCC
	4B						middle	depr	mm	mod SCC
	4C						middle	flat	ep	mod SCC
5	5A	M	62	none	CC	other disease	lower	depr	ep	mod SCC
	5B						middle	depr	mm	mod SCC
6	6A	M	62	none	none	other disease	middle	depr	ep	mod SCC
	6B						middle	flat	mm	mod SCC
7	7	M	70	none	Ileus	other disease	lower	depr	ep	mod SCC
8	8	M	46	pain	none	symptoms	middle	elev	mm	mod SCC
9	9	M	72	SGC	GC	other disease	middle	depr	mm	mod SCC
10	10	M	77	smart	none	symptoms	middle	flat	mm	mod SCC
11	11	M	60	fullness	LC	symptoms	upper	elev	mm	por SCC

M, male; F, female, SGC, symptoms caused by gastric cancer; GC, gastric cancer; CC, colon cancer; LC, liver cirrhosis; depr, depressed; elev, elevated; mod SCC, moderately differentiated squamous-cell carcinoma; por SCC, poorly differentiated squamous-cell carcinoma.

was also performed on all the patients, except for patient 11. The resected specimen was dyed with Lugol solution immediately after resection. Thereafter the specimen was stretched appropriately on a board with pins and fixed with 10% formalin. Several days later the specimen was again dyed with Lugol solution and photographed. Subsequently the specimen was serially sectioned into blocks 5 mm wide and 4 cm long. One slide from each block was stained with hematoxylin and eosin (H&E) and periodic acid–Schiff (PAS) for histologic examination. We conducted a comparative study on radiography, conventional endoscopy, dye endoscopy, biopsy, and postoperative histology by H&E and PAS.

Results

Table 2 shows diagnostic process of the 11 patients, arranged in order of the depth and size of the cancer. Only six patients (54.5%) showed symptoms that might be related to the upper alimentary tract, and the remaining five patients were asymptomatic. Of the six symptomatic patients, two had coexisting advanced gastric carcinoma, and their symptoms seemed to be caused by this carcinoma. Consequently only four patients (36.3%) showed the esophageal symptoms (2 patients had smart feeling, 1 patient had epigastric pain, and 1 patient had a sense of fullness). These four patients were associated with mucosal cancer of 2 cm or larger. Including the two patients showing symptoms caused by gastric cancer, the seven other patients (63.6%) free of esophageal symptoms were diagnosed by chance; one patient was diagnosed by a thorough medical examination, and the remaining six were diagnosed when they underwent an examination for another digestive disease. Among the 18 lesions, the sites of two lesions (2C and 2D) were not exposed on radiography or endoscopy.

Figure 1 shows the relationship between pathology (size and depth of transmural invasion) and radiographic findings in 16 lesions. Six (85.7%) of seven mm cancers showed any of the following radiographic findings, regardless of size: rigidity of the wall, irregularity of the margin, and thin barium fleck. Among the six lesions, the smallest measured 7 mm × 4 mm. No abnormal findings were recognized on radiography in three ep cancers less than 2 cm in size. On the contrary abnormal radiographic findings were shown on four of five (80%) ep cancers of 2 cm or more in size, suggesting that even in ep cancers those with a considerable size often yield some radiographic findings.

Figure 2 shows the relationship between pathology and endoscopic findings of the 16 lesions. All 15 lesions showed abnormal endoscopic findings, regardless of the size and depth of transmural invasion, except for one lesion (Table 2, lesion 4C) that was detected only by post-

TABLE 2. *Pathohistology and Findings in Radiography, Conventional Endoscopy, and Dye Endoscopy in 18 Mucosal Esophageal Cancers*

					Endoscopic Findings		
Lesion	Gross Type	Depth of Cancer	Size (cm)	Radiographic Findings	Morphologic Change	Color Change	Findings of Dye Endoscopy
4C	flat	ep	0.5 × 0.3	np	no findings		unstained
1	flat	ep	1.0 × 0.4	np		redness, PB	unstained
2A	flat	ep	1.0 × 0.7	np	elevation	redness	unstained
2B	flat	ep	1.3 × 1.0	np		redness	unstained
3	flat	ep	2.0 × 1.0	BF, RW, DL	TA		unstained
4A	flat	ep	2.5 × 1.0	np		redness	unstained
5A	depr	ep	3.0 × 2.0	RW	depression	redness	unstained
6A	depr	ep	3.0 × 2.5	RW	depression	redness	unstained
2C	flat	ep	3.5 × 1.8	not exposed	not exposed		unstained
7	depr	ep	3.5 × 2.5	BF	irregularity		unstained
4B	depr	mm	0.7 × 0.4	RW	depression		unstained
6B	flat	mm	1.5 × 1.5	RW		redness	unstained
2D	flat	mm	2.0 × 1.0	not exposed	not exposed		unstained
8	elev	mm	2.0 × 1.2	RW		redness	unstained
5B	depr	mm	2.2 × 1.6	RW	depression	redness	unstained
9	depr	mm	2.5 × 1.5	np	depression	redness	unstained
10	flat	mm	4.0 × 2.2	RW, IM		redness	unstained
11	elev	mm	5.0 × 4.0	RW	elevation	discoloration	not done

depr, depressed; elev, elevated; BF, barium fleck; RW, rigidity of the wall; DL, doubled line; np, nothing particular; IM, irregularity of the margin; PB, punctate bleeding; TA, transformation of the arc.

operative pathohistology of the specimen. Of the 15 lesions detected before operation, only 9 (60%) showed morphologic changes, while 13 (86.7%) showed color changes. Of the 9 lesions associated with morphologic change, 5 were observed as slight depression, 1 as roughness (irregularity) of the mucosal surface, 1 as slight elevation, and 1 as transformation of the arc (Fig. 3A) of the esophagus. Color change (redness) (Fig. 3A) was seen in 12 lesions (80%); discoloration appeared in 1 lesion; and punctate bleeding was visible in 1 lesion.

Dye endoscopy before operation and dyeing of the resected specimen visualized all 18 lesions as unstained areas—those showing neither morphologic nor color change, as well as those showing both or either of them in conventional endoscopy.

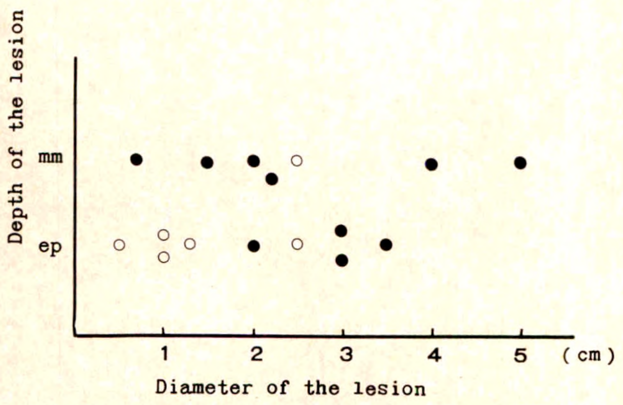


FIG. 1. Relationship between pathology (size and depth of transmural invasion) and radiographic findings in 16 lesions. •, a lesion showing findings; ○, a lesion without findings.

Case Reports

Case 1

This case (Table 2, lesion 3) was the smallest lesion that was detected by radiographic examination. The lesion diameter measured 2 cm and was ep cancer located in the middle esophagus. In radiography (Fig. 4) bending appearance (indicated by a forked arrow) due to rigidity of the wall was seen. In addition thin barium flecks (indicated by the other arrow in Fig. 4) were seen near this bending. Conventional endoscopy (Fig. 4A) revealed ill-circumscribed redness accompanied by mild transformation of the arc. Dye endoscopy (Fig. 3B) by Lugol solution demonstrated this lesion as a well-circumscribed unstained area.

Case 2

This case (Table 2, lesion 1) was a flat lesion measuring 1 cm in diameter and was ep cancer located in the lower esophagus. No abnormal

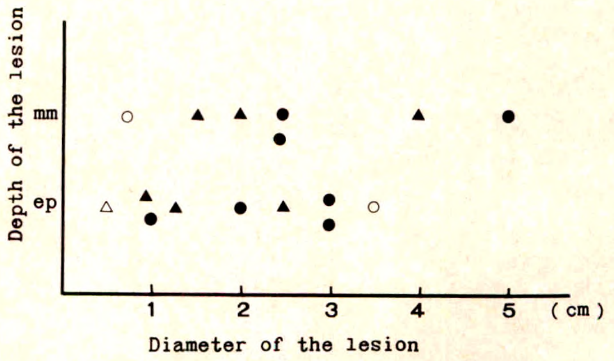
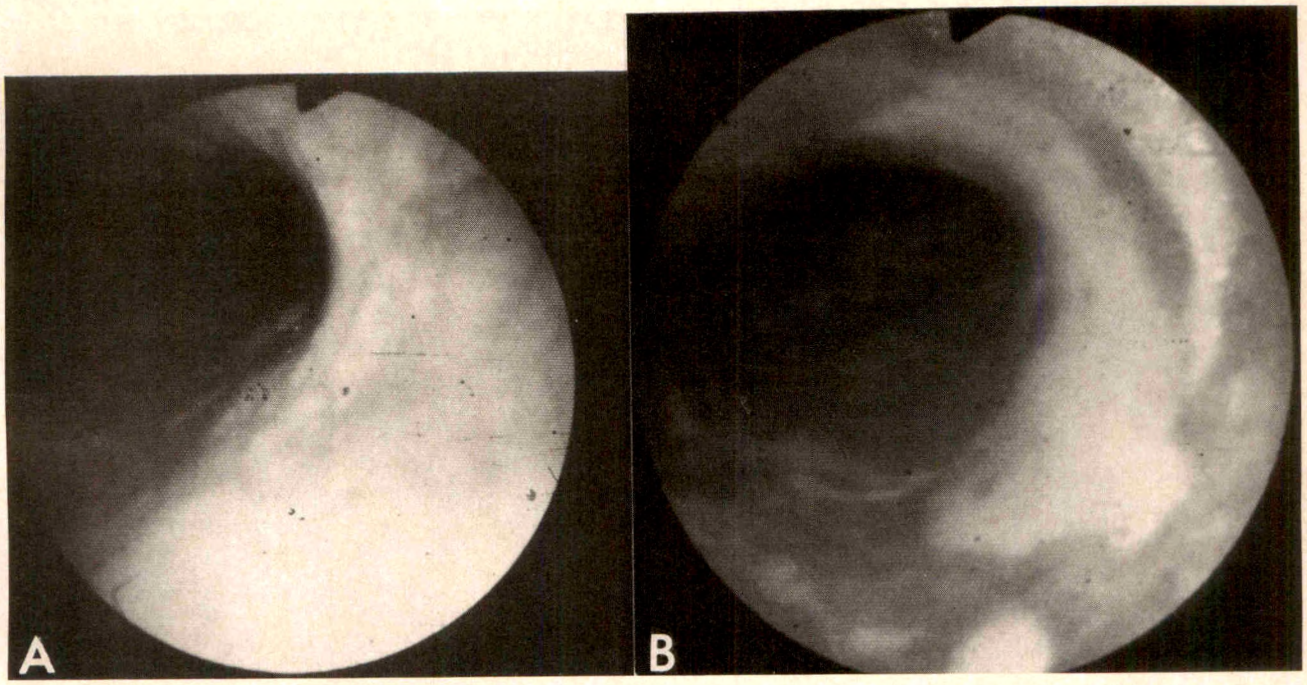


FIG. 2. Relationship between pathology and endoscopic findings of 16 lesions. •, a lesion showing both morphologic and color changes; ○, a lesion showing morphologic change but not color changes; ▲, a lesion showing color change but not morphologic changes; △, a lesion showing neither morphologic nor color change.



FIGS. 3A and B. Conventional endoscopy (A) and dye endoscopy (B) with Lugol solution performed on Case I (lesion 3 in Table 2).

findings were found in radiography. This was the smallest ep cancer that was detected by conventional endoscopy and confirmed by dye endoscopy. A well-circumscribed reddened area associated with punctate bleeding was found in conventional endoscopy (Fig. 5A). However no morphologic change was noted in conventional endoscopy (Fig. 5A) or the resected specimen (Fig. 6A). This lesion was confirmed as a well-circumscribed unstained area by dye-endoscopy (Fig. 5B) and on the resected specimen (Fig. 6B) that was dyed with Lugol solution.

Case 3

This case (Table 2, lesions 4A to 4C) included three cancerous lesions, one of which was recognized only by postoperative histology. Retrospectively we also identified it by dye endoscopy, but not by radiography or conventional endoscopy. Conventional endoscopy (Fig. 7A) demonstrated a reddened area (indicated by an arrow), lesion A, which was not identified by radiography. This lesion was confirmed by dye endoscopy to be an unstained area. Apart from lesion A, conventional endoscopy (Fig. 8A) disclosed a shallow and well-circumscribed depression (as indicated by arrow A), lesion B, which showed rigidity of the wall on radiography. Lesion B was also confirmed by dye endoscopy to be a well-circumscribed unstained area (Fig. 8B). Both unstained areas, which were almost the same as the areas determined histologically, were wider than the depressions seen in conventional endoscopy. This result indicates that dyeing with solution leads to more accurate evaluation of the range of the lesion. In addition to the two lesions, a small unstained area (indicated by arrow C) was found by dye endoscopy (Fig. 8B); this lesion showed no abnormal findings on conventional endoscopy (Fig. 8A). Lesion C, however, had been overlooked before operation and was retrospectively identified. On the resected specimen (Fig. 9), all three lesions were unstained by Lugol solution. The unstained area of lesion C measured 3 mm and histologically was minute ep cancer (Fig. 10) of the same size.

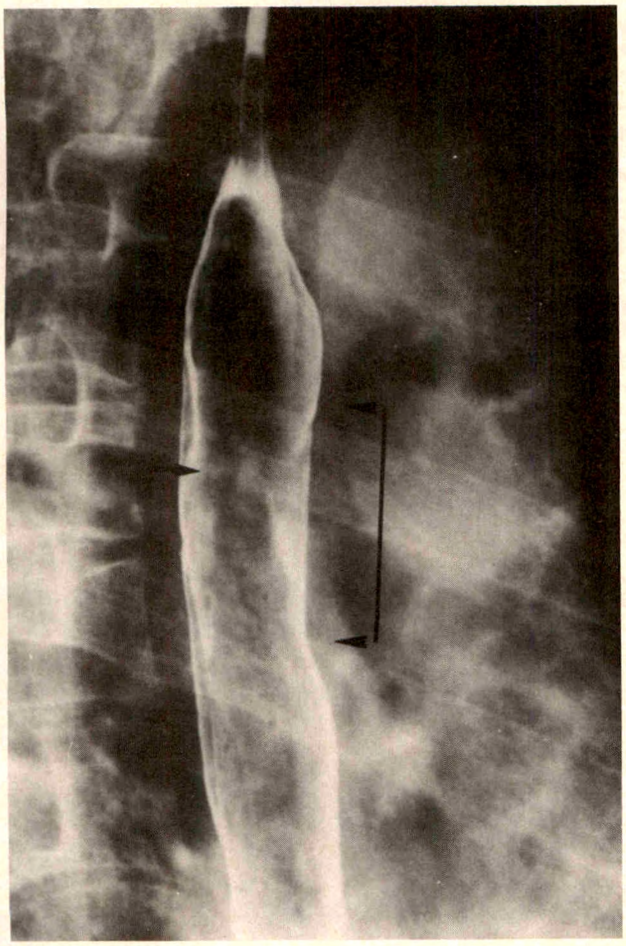
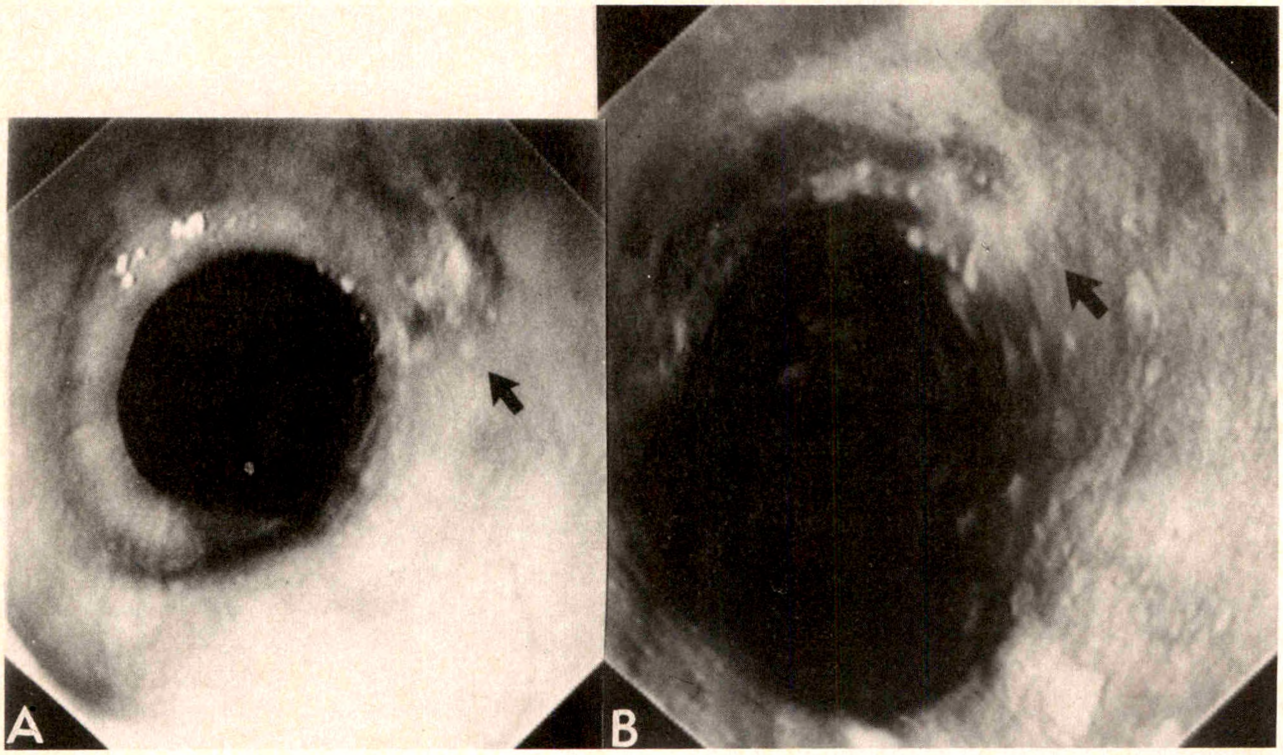


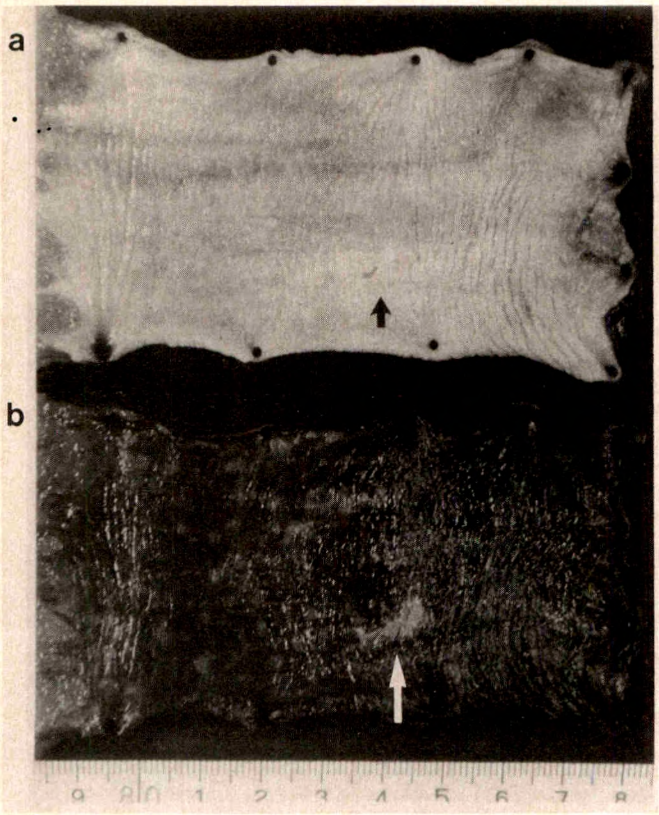
FIG. 4. Radiography of case 1 (Table 2, lesion 3). A forked arrow indicates a bending appearance, and the other arrow indicates a barium fleck.

Discussion

Superficial esophageal cancer causes no symptoms in 20% to 40% of patients and, when asymptomatic, it is



FIGS. 5A and B. Conventional endoscopy (A) and dye endoscopy (B) with Lugol solution performed on case 2 (Table 2, lesion 1).

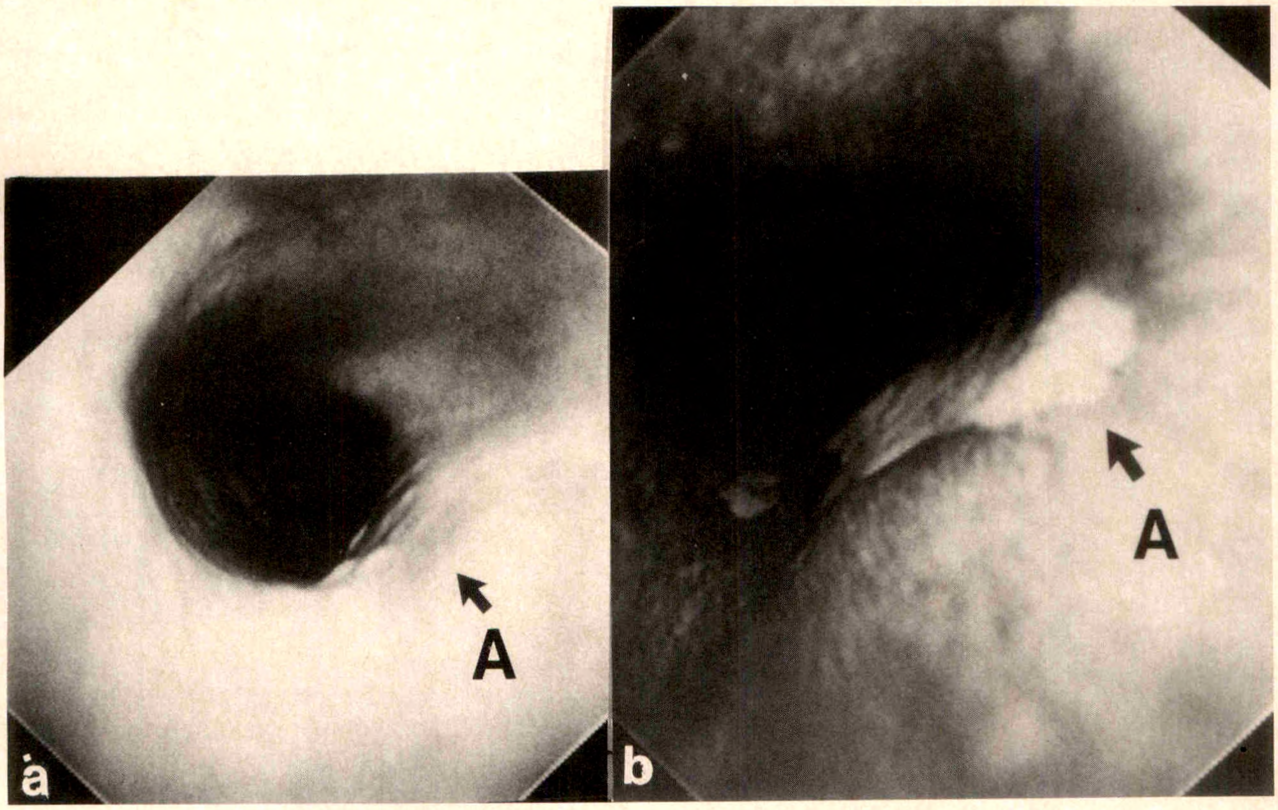


FIGS. 6A and B. The resected specimen before (A), and after (B) dyed with Lugol solution in case 2.

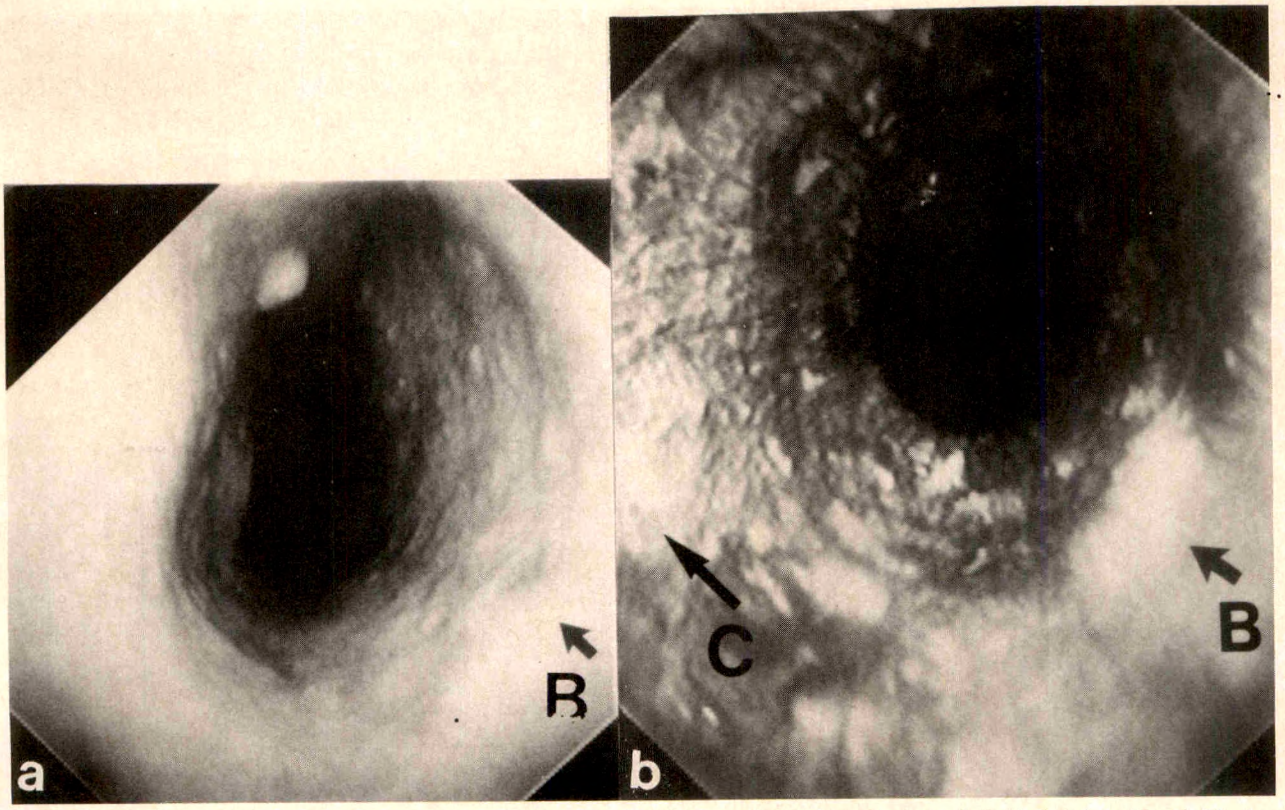
detected during examination for another disease or periodic check-up.[8–10] Statistics found by Nabeya et al.[11] on Japanese patients revealed that only 16% of early esophageal cancers elicited symptoms such as severe disturbance of swallowing and passage, and that about 40% of early esophageal cancers were discovered without symptoms. In this series only 6 (54.5%) of 11 patients complained of symptoms. Furthermore two of the six patients had concomitant advanced gastric carcinoma, and their symptoms seemed to be derived from gastric carcinoma. Consequently only four patients (36.3%) showed esophageal symptoms.

Radiography and endoscopy are the main diagnostic aids for the disease. Recently discovery of the cancer by endoscopy, particularly by panendoscope, has increased.[12] Diagnostic ability of radiography in early esophageal cancer [8,10,13,14] has been investigated for more than 20 years. Sato et al.[10] stated that minute lesions as small as 5 mm were impossible to identify. In this study 75% of mm cancers yielded radiographic findings regardless of size; the smallest esophageal mm cancer (Table 2, lesion 3 [Case 1]) that we detected radiographically measured 7 × 4 mm. Furthermore this study showed that radiography possibly identifies ep cancer if it is 2 cm or more in size. However detection and diagnosis of minute esophageal cancer are still difficult by radiography.[4]

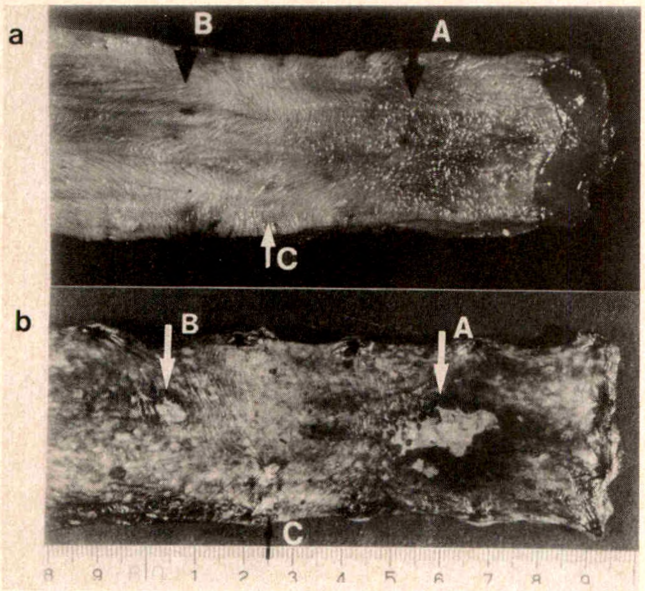
Minute esophageal cancers are identified endscopically



FIGS. 7A and B. Conventional endoscopy (A) and dye-endoscopy (B) with Lugol solution performed on case 3 (Table 2, lesion 4A). Each arrow indicates lesion A.



FIGS. 8A and B. Conventional endoscopy (A) and dye endoscopy (B) with Lugol solution performed on case 3 (Table 2, lesions 4B and 4C). Arrows B and C indicate lesions B and C.



FIGS. 9A and B. The resected specimen before (A), and after (B) dyed with Lugol solution in case 3. Arrows A, B, and C indicate lesions A, B, and C.

by such characteristics as shallow depression, slight elevation (like a flat board), redness, or discoloration.[4] Endo et al.[15] emphasized that induction of the panendoscope affords the detection of minute lesions as small as 2 to 3 mm. In this series conventional endoscopy showed a high rate (83%) of abnormal findings. Morphologic changes accompanying mucosal cancers are usually shallow depression or slight elevation and color change (redness). Lesion 1 in Table 2 (Case 2) was the smallest ep cancer that was discovered with conventional endoscopy. This lesion was observed as well-circumscribed redness accompanied by punctate hemorrhage in the absence of morphologic change.

In the present study Lugol solution applied on dye endoscopy and on the dyeing of the resected specimen visualized all the lesions as well-circumscribed and even unstained areas. Lesion C (Case 3), which measures 3 mm, especially illustrates the high availability of the dye endoscopy.

The esophageal Lugol test originates in a color reaction between the glycogen within the tissue and iodine. The amount of glycogen within the tissue relates to the intensity of this reaction.[16] Mature nonkeratosic squamous epithelial cells contain a large amount of glycogen. In the normal mucosa this glycogen reacts with iodine to produce the staining in black-brown or green-brown, while an area that does not contain glycogen is unstained. The contrast between the two facilitates the evaluation of the differences in characteristics of the mucosa. Schiller[17] stated that glycogen disappears in the carcinomatous layer, not only in the superficial part but also in the down growth and extension in the epithelium, forming an unstained area. Brodmerkel[18] reported that esophagitis is less stained in accordance with the extent of exfoliation of the epithelium and that necrotic tissue at the ulcer base is unstained. We observed that each area where PAS reaction was weak or negative was equivalent to an unstained area in the esophageal mucosa with Lugol solution, and that an unstained area of the resected specimen dyed with Lugol solution coincided completely with a histologically determined cancerous area.[19]

With Lugol solution the normal stratified squamous epithelium is stained in black-brown (normally stained area), while the cancerous lesion is almost unstained (unstained area).[16,20] Intermediate to these two is a lightly stained area. The atypia of this area varies.[21] On the other hand glycogen acanthosis, one of so-called small leukoplakia,[18,21] and some hyperplasia[21] of considerable exten-

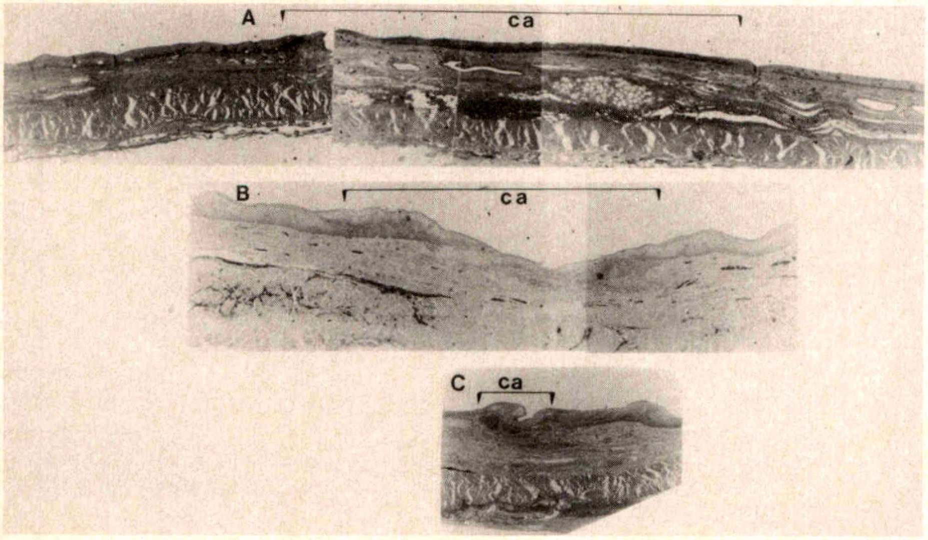


FIG. 10. Photomicrograph showing three lesions (A–C) of case 3. Arrows A, B, and C indicate lesions A, B, and C.

sion are stained more darkly than normal with Lugol solution.

In addition to cancer, unstained esophageal mucosal lesions include esophagitis, edema, mucosal atrophy, severe inflammation, dysplastic epithelium, erosion, ulcer, and ectopic mucosa.[22,23] Therefore unstained esophageal lesions are not exclusive to esophageal cancer. However if biopsy is combined for such a lesion, the diagnostic accuracy would surely increase. Furthermore, as illustrated in this study, unstained areas of cancerous lesions agreed much more than areas of cancer observed by conventional endoscopy.

In conclusion endoscopy is more helpful than radiography in the diagnosis of esophageal mucosal cancer. Particularly dye endoscopy using Lugol solution is very important because of easier detection of minute or superficial esophageal cancer and easier evaluation of the extent of the lesion.

Acknowledgments

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Neutrophil-Dependent, Oxygen-Radical Mediated Lung Injury Associated with Acute Pancreatitis

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Cerulein-induced acute pancreatitis in rats is associated with a reversible lung injury that is characterized by alveolar capillary endothelial-cell injury, increased microvascular permeability, interstitial edema formation, and intraalveolar hemorrhage and fibrin deposition. The role of mediators in this injury was analyzed using gravimetric data, microvascular permeability indices, electron microscopy, and a quantitative morphometric analysis. Neutrophil depletion induced by a specific antibody was highly protective against lung injury. Interruption of the complement pathway (using low dose *Naja naja* cobra venom factor) also protected against lung injury. Catalase and superoxide dismutase were also protective. The iron chelator deferoxamine and the hydroxyl radical scavenger, dimethylsulfoxide, were not protective against acute lung injury. These data suggest that complement, neutrophils, and neutrophil-derived (H_2O_2-dependent) oxygen products mediate lung injury that occurs secondary to cerulein-induced pancreatitis. In contrast to other models of neutrophil-dependent, oxygen-radical-mediated lung injury, this lung injury does not appear to be an iron-dependent and hydroxyl-radical mediated injury. We postulate that the process of acute pancreatitis leads to complement activation followed by neutrophil recruitment, sequestration, and adherence to alveolar capillary endothelial cells. Ultimately lung injury appears to result from local endothelial-cell injury secondary to neutrophil-generated oxygen products that may be myeloperoxidase dependent.

PULMONARY DYSFUNCTION ASSOCIATED with acute pancreatitis occurs in as many as 50% to 70% of human patients.[1,2] Symptoms are most frequently tachypnea or mild hypoxemia and the underlying lung injury appears mild and generally reversible.[3] In approximately one third of patients the lung injury is progressive and may be associated with acute respiratory failure and fully developed Adult Respiratory Distress Syndrome (ARDS).[1] The events that discriminate between these outcomes are not fully understood. However it is probable that a variety of host responses and external events determine the development of this lung injury.

We have recently characterized in rats a reversible acute lung injury occurring secondary to acute pancreatitis.[4] The model uses cerulein-induced acute pancreatitis and is associated with an acute alveolar capillary endothelial-cell injury. The injury is not attributable to cerulein itself and appears to share some of the features of human ARDS, including increased microvascular permeability in the lung, interstitial edema formation, infiltration of neutrophils and prominence of macrophages, intraalveolar hemorrhage and fibrin deposition, and endothelial-cell injury. At the ultrastructural level separation of the endothelial cell from the basement membrane occurs and even cell death is observed.

The features of increased microvascular permeability and morphologic evidence of injury are shared with a number of other experimental animal models of acute lung injury[5-7] and with human ARDS associated with pancreatitis.[8-10] This series of experiments was designed to evaluate the role of the complement system, neutrophils, and neutrophil-derived oxygen-free radicals in the pathogenesis of acute lung injury after cerulein-induced pancreatitis.

Materials and Methods

Animal Model

Male pathogen-free Sprague-Dawley rats (200 to 250 gm; Charles River, Portage, MI) were used for all experiments. Protocols were approved by the University of Michigan Animal Subjects Review Committee. Anesthesia was induced with subcutaneous administration of

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ketamine hydrochloride (100 mg/kg body weight). Silastic (TM) (Dow Corning, Midland, MI) catheters (0.20 mm internal diameter) were placed by cutdown into the jugular vein under sterile conditions. The catheters were tunneled subcutaneously to exit in the dorsal cervical region of each rat. Each catheter was secured, flushed with sterile physiologic saline, and capped. The rats were allowed to recover overnight in individual cages and had free access to food and water. Infusion of cerulein (Sigma Chemical, St. Louis, MO) or physiologic saline was performed the following day. Sterile physiologic saline was used for the preparation of the cerulein infusate as well as for infusion of control animals. The dose of cerulein was 5 μg/kg/hr as described by Lampel and Kern.[11] The infusion apparatus consisted of stainless steel wrapped intravenous (IV) tubing connected to 20-mL syringes. Before infusion catheters were flushed with sterile physiologic saline (0.5 to 1.0 mL) to insure patency. Continuous individual intravenous infusions were given using infusion pumps (Harvard, Pump 22, South Natick, MA) at an infusion rate of 2 mL per hour for three hours. Immediately before infusion an intravenous bolus of ^{125}I-bovine serum albumin (BSA) (800,000 cpm) was given to allow assessment of microvascular permeability changes. After infusion the rats were sedated with ketamine hydrochloride (50 mg/kg body weight, i.p.).

At sacrifice laparotomy was performed on anesthetized rats, 1 mL of blood was aspirated from the inferior vena cava and then transected, resulting in exsanguination. The heart and lungs were removed *en bloc* and 10 mL of sterile saline was infused into the right ventricle to wash residual blood and ^{125}I-BSA from the pulmonary vascular bed. When done rapidly a spontaneous heart beat persists and the lung parenchyma develops a typical white blanched appearance when bloodless. The whole lungs were then weighed and evaluated in a gamma scintillation counter with the 1-mL blood sample. The ratio of lung-to-blood counts was taken as a measure of microvascular permeability and has been shown to be a reliable, quantifiable marker of lung injury in this as well as other lung-injury models.[5,6] This aspect of the permeability assessment is described in detail in several recent publications.[4–6]

In addition the pancreatic capillary permeability changes were determined. The pancreas was quickly dissected, blotted, weighed, and counted along with each animal's lungs and blood in a gamma scintillation counter. The ratio of pancreas-to-blood counts in this case represents pancreatic microvascular permeability and reflects one component of acute pancreatitis edema formation.

Interventions

Specific interventions were designed to assess the involvement of complement, neutrophils, and oxygen-derived free radicals.

(1) Complement depletion was accomplished by intraperitoneal injection of cobra venom factor (purified from *Naja naja* venom[12]) at a dose of 50 units per rat for each of 2 days before the experiment. This treatment regimen results in nearly complete depletion of C3 and does not, *per se*, produce acute lung injury.[5]

(2) Neutrophil depletion was achieved by intraperitoneal injection of rabbit anti-rat neutrophil antiserum (0.5 mL/100 gm body weight) 24 hours before infusion with cerulein or normal saline. Within 18 hours this specific antiserum results in a drastic reduction in peripheral blood neutrophil counts (less than 250 neutrophils/mL). Before infusion, blood samples from each rat were obtained and total neutrophil counts were done. Only those rats with counts of less than 250 neutrophils/mL were used for subsequent experiments.

(3) Superoxide dismutase (SOD; Sigma, St. Louis, MO) was given as an intravenous bolus (20 mg) before each experiment and was followed by a continuous infusion (10 mg/hr) given simultaneously with the cerulein or normal saline infusion.

(4) Polyethylene glycol conjugated SOD (PEG-SOD; Enzon, Fairlawn, NJ) was given as a single intravenous bolus (25,000 μ) before infusion with cerulein or normal saline.

(5) Catalase (CAT; Sigma, St. Louis, MO) was given in a manner similar to SOD (20 mg IV bolus followed by continuous infusion of 10 mg/hr).

(6) PEG-catalase (PEG-CAT; Enzon, Fairlawn, NJ) was given as a single bolus of 25,000 μ IV before infusion with cerulein or normal saline.

(7) Deferoxamine mesylate (Ciba-Geigy, Summit, NJ) was given as a single IV bolus of 5 mg/kg before infusion with cerulein or normal saline.

TABLE 1. *Wet Lung Weights in Rats with Cerulein-Induced Pancreatitis*

Intervention	Wet Lung Weights	p value*
None	0.51 ± 0.01 (32)	—
SOD	0.34 ± 0.01 (5)	$<10^{-6}$
PEG-SOD	0.36 ± 0.01 (6)	$<10^{-6}$
CAT	0.44 ± 0.01 (6)	0.006
PEG-CAT	0.47 ± 0.01 (7)	0.078
Neutrophil depletion	0.43 ± 0.01 (6)	0.002
Deferoxamine	0.55 ± 0.05 (8)	0.209
Dimethylsulfoxide	0.59 ± 0.06 (7)	0.025

Saline-infused control weights = 0.35 ± 0.02.
Wet lung weights expressed as % total body weight (mean ± SEM).
* Statistical analysis by Student's t test; animals with cerulein-induced pancreatitis and antioxidant intervention compared to cerulein-induced pancreatitis with no antioxidant intervention.
SOD, superoxide dismutase.
PEG-SOD, polyethylene glycol conjugated SOD.
CAT, catalase.
PEG-CAT, PEG-catalase.

(8) Dimethylsulfoxide (DMSO; Fisher, Fairlawn, NJ) was given as an intraperitoneal bolus of 1.5 mL per kg before cerulein or normal saline infusion.

Morphologic Studies

For histologic study rats were prepared identically with either cerulein or saline infusion. ^{125}I-BSA injections were omitted. The pancreas was quickly dissected and placed in 4% glutaraldehyde in cacodylate buffer. At sacrifice the lungs were inflated *via* the trachea with 4% glutaraldehyde in cacodylate buffer. At each time point evaluated, at least five animals per group were assessed histologically. After fixation biopsies were taken from each lobe of the lung and embedded in epon. For light microscopy studies 1-μm sections were taken from the plastic blocks and stained with toluidine blue. For electron microscopy, ultrathin sections were cut and processed for ultrastructural analysis using a Philips 401 transmission electron microscope (Philips Co., Amsterdam, The Netherlands). For morphometric analysis, plastic embedded sections (1 μm thick) of lung tissue stained with toluidine blue were prepared as described above. A minimum of 60 different interstitial capillaries and alveoli from each of five rats per group were examined by morphometric techniques using an Olympus microscope with a 40x objective (Olympus, Tokyo, Japan). The numbers of neutrophils per 40x power field were determined for each section. Details of these techniques have been previously published.[7]

Amylase/Lipase Measurement

Serum amylase and lipase were assessed by the clinical chemistry laboratory in the Department of Pathology using the DuPont aca analyzer. Amylase is measured by the hydrolysis of the substrate maltopentose.[13] Lipase is determined by turbidity measurements using triolein as the substrate.[14,15]

Myeloperoxidase Assay

A time-course study to determine the amount of myeloperoxidase in lung tissue was done by infusing rats with cerulein or normal saline for 30 minutes, 3 hours, and 6 hours. At sacrifice washed lung parenchyma was weighed and then homogenized in phosphate buffer. The amount of myeloperoxidase present was determined spectrophotometrically using O-dianisidine dihydrochloride.[16,17]

Results

The body, wet lung, and wet pancreas weights for each rat were obtained. Wet lung and wet pancreas weights

TABLE 2. *Pancreas Microvascular Permeability Indices and Weights, Serum Amylase, and Lipase in Rats with Cerulein-Induced Pancreatitis*

	Saline-Infused Controls					Cerulein-Induced Pancreatitis				
Intervention	PI	Wt	Amylase	Lipase	(n)	PI	Wt	Amylase	Lipase	(n)
None	0.13 ± 0.02	0.30 ± 0.01	549 ± 40	<1	(6)	0.92 ± 0.12†	0.84 ± 0.10†	3516 ± 364†	467 ± 49†	(18)
SOD	0.12 ± 0.01	0.21 ± 0.02	533 ± 107	<1	(6)	0.86 ± 0.17†	0.47 ± 0.05†	7465 ± 959†	816 ± 69*†	(5)
PEG-SOD	0.13 ± 0.02	0.20 ± 0.02	799 ± 112	<1	(5)	0.88 ± 0.21†	0.50 ± 0.04†	2724 ± 158†	346 ± 42†	(5)
CAT	0.11 ± 0.02	0.29 ± 0.01	516 ± 44	<1	(5)	0.23 ± 0.04*	0.35 ± 0.04*	4957 ± 610*†	605 ± 37†	(9)
PEG-CAT	0.11 ± 0.03	0.32 ± 0.01	657 ± 45	<1	(9)	0.93 ± 0.28†	0.90 ± 0.14†	2644 ± 371†	358 ± 37†	(7)
Neutrophil depleted	0.11 ± 0.01	0.31 ± 0.02	942 ± 114	<1	(4)	0.41 ± 0.07*†	0.48 ± 0.01†	4355 ± 414†	306 ± 42†	(6)
Complement depleted	0.17 ± 0.01	—	815 ± 80	<1	(8)	0.28 ± 0.03*†	—	5679 ± 663*†	520 ± 57†	(16)
Deferoxamine	0.07 ± 0.01	0.28 ± 0.01	—	—	(3)	1.02 ± 0.29†	0.96 ± 0.15†	—	—	(8)
Dimethylsulfoxide	0.10 ± 0.01	0.32 ± 0.02	—	—	(12)	0.92 ± 0.08†	0.77 ± 0.07†	—	—	(8)

Wt, pancreatic wet weight expressed as percent total body weight.

PI, Microvascular Permeability Index expressed as pancreas/blood cpm

* $p < 0.05$, comparing groups with cerulein-induced pancreatitis and antioxidant interventions to similar animals with no antioxidant intervention; Student's t test (data expressed as means ± SEM).

† $p < 0.05$, comparing groups with cerulein-induced pancreatitis to appropriate saline controls; Student's t test (data expressed as means ± SEM).

SOD, superoxide dismutase.

PEG-SOD, polyethylene glycol SOD.

CAT, catalase.

PEG-CAT, PEG catalase.

TABLE 3. *Lung Microvascular Permeability Indices in Rats with Cerulein-Induced Pancreatitis*

Intervention	Lung Permeability Index*	p value†
None	0.24 ± 0.04 (32)	—
SOD	0.02 ± 0.05 (5)	0.030
PEG-SOD	0.03 ± 0.04 (5)	0.040
CAT	0.07 ± 0.02 (16)	0.004
PEG-CAT	0.07 ± 0.01 (7)	0.051
Neutrophil depletion	0.02 ± 0.03 (6)	0.001
Complement depletion	0.02 ± 0.04 (15)	0.020
Deferoxamine	0.11 ± 0.06 (8)	0.138
Dimethylsulfoxide	0.35 ± 0.09 (7)	0.221

* Permeability indices reported as normalized values (experimental minus paired saline-infused control). Index calculated as lung/blood cpm (see text for description) (mean ± SEM).

† Statistical analysis by Student's t test, animals with cerulein-induced pancreatitis and antioxidant intervention compared to no antioxidant intervention.

SOD, superoxide dismutase.

PEG-SOD, polyethylene glycol conjugated SOD.

CAT, catalase.

PEG-CAT, PEG catalase.

were expressed as a percentage of total body weight and are summarized for each treatment group. Lung and pancreas gravimetric data are included in Tables 1 and 2.

Microvascular permeability indices are presented in Tables 2 and 3.. The data are expressed as the ratio of lung counts or pancreas counts compared to a reference of counts per 1 mL of blood. This eliminates the variability inherent in injecting small volumes of a tracer and provides data that are intuitively interpretable. A ratio of 0.20, for example, indicates that an equivalent of 20% of the intravascular ^{125}I label in 1.0 mL blood has been sequestered in the extravascular compartment of lung or pancreas. For reference purposes the permeability values obtained in normal, saline-infused, intact rat lungs and pancreas are less than 0.1 to 0.2.[4,18]

Requirement for Neutrophils in Acute Lung Injury After Pancreatitis

Rats not subjected to neutrophil depletion procedures developed significant increases in lung wet weights (Table 1; 0.35% ± 0.02% *versus* 0.51% ± 0.01% of total body weight; $p < 0.05$ compared to saline-infused controls) and in lung microvascular permeability indices (0.30% ± 0.02% *versus* 0.54% ± 0.04%; $p < 0.003$ compared to controls) after cerulein production of acute pancreatitis. Neutrophil depletion was protective against permeability changes and increases in wet weights as shown in Tables 1 and 3. The wet lung weight was significantly lower (0.43% ± .01%, $p = 0.002$) in neutrophil-depleted animals than in neutrophil-intact animals, and the increase in the microvascular permeability index was significantly less (0.02% ± 0.03%, $p = 0.001$) in neutrophil-depleted animals with pancreatitis than in neutrophil-intact animals.

It is important to note that cerulein infusion did result in the development of acute pancreatitis in neutrophil-depleted animals as defined by increases in serum enzyme content, although there was some attenuation in the permeability index in the pancreas (Table 2). Although neutrophil-depleted animals had less edema formation in the pancreas after infusion of cerulein, pancreatic weight and ^{125}I BSA leak were significantly elevated compared to neutrophil-depleted saline-infused controls. The observations that neutrophil depletion prevents lung injury but not the development of acute pancreatitis suggest that the protection against lung injury in the depleted animals results from lack of availability of neutrophils rather than prevention of pancreatic injury.

Evidence for the sequestration of neutrophils in the injured lung after induction of acute pancreatitis by infusion of cerulein is suggested by myeloperoxidase measurements in lung tissue (Fig. 1). Myeloperoxidase is an unequivocal measurement of neutrophil accumulation in tissue. There was a twofold increase in myeloperoxidase extractable from the lung tissue after the induction of acute pancreatitis. It can be calculated on the basis of myeloperoxidase content in rat neutrophils that this represents (as a minimal estimate) the presence in lung of 6.23×10^6 neutrophils per gram of tissue (compared to 2.68×10^6 neutrophils/gram in saline-infused lungs). These findings confirm the presence of neutrophils in injured lungs and support the concept that their presence is related to the induction of lung injury.

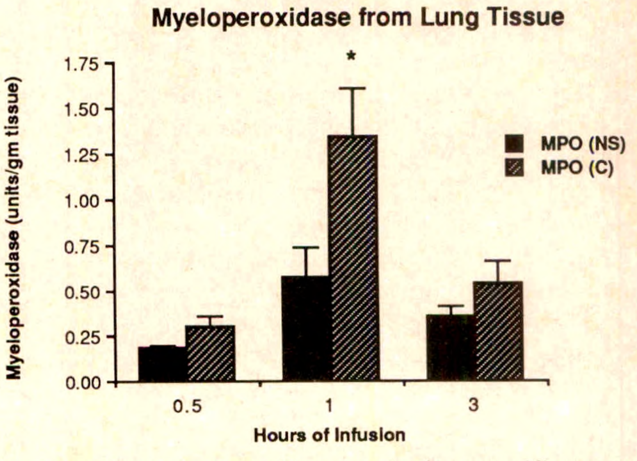


FIG. 1. Lung-tissue myeloperoxidase, a marker for neutrophil accumulation in alveolar capillaries, is illustrated. A significant accumulation of neutrophils occurs after one hour of cerulein infusion. (* $p < 0.05$, Students t test, compared to paired saline control.)

Complement Requirement for Lung Injury After Induction of Acute Pancreatitis

In rats with an intact complement system, cerulein-induced pancreatitis generated an increase in the lung microvascular permeability index (Table 3; 0.24% ± 0.04%) that was significantly different ($p < 0.05$) from values obtained in saline-infused animals. Rats depleted of complement exhibited little evidence of alveolar endothelial-cell injury and microvascular leak after induction of pancreatitis (microvascular permeability index increase 0.02 ± 0.14, p = 0.02) compared to complement intact animals with pancreatitis.

It is important to emphasize that pancreatic edema formation (permeability index) was diminished in cerulein-treated animals that were complement depleted (Table 2), but ^{125}I BSA sequestration was still significantly ($p<0.05$) elevated and serum lipase and amylase levels were not reduced as a result of complement depletion in cerulein-infused rats (Table 2). Therefore complement depletion appears protective against lung injury but does not protect against pancreatic acinar-cell injury.

Evidence that Lung Injury Is Dependent on Formation of H_2O_2

Both SOD and PEG-SOD pretreatment prevented lung weight increases and microvascular permeability increases in the lung after cerulein-induced acute pancreatitis (Tables 1 and 3). A similar protective effect was evident for CAT- and PEG-CAT-treated animals, although in PEG-CAT-treated animals the degree of protection was of borderline statistical significance (p = 0.051 for lung permeability index, p = 0.078 for wet lung weights). Figure 2 illustrates the proposed chemical pathways involved and the points for antioxidant interventions. The observation that catalase protects against interstitial edema formation in the lung indicates that H_2O_2 or its conversion products contribute to lung injury.

While treatment of rats with antioxidant enzymes was protective against development of lung injury, the same interventions had no consistent effects on permeability changes in the pancreas or increases in levels of serum enzymes after infusion of cerulein (Table 2). In animals with cerulein-induced pancreatitis, pancreatic edema formation was diminished by continuous catalase infusion, but serum amylase and lipase remained significantly elevated ($p <0.05$) compared to saline controls. The other antioxidant regimens SOD, PEG-SOD, and PEG-catalase did not prevent either pancreatic edema formation or elevation of serum amylase and lipase but were protective against the lung injury. We have recently inferred that the effects of PEG-conjugated antioxidants are restricted to the intravascular compartment as a result of their large molecular size.[18] Because neutrophils are sequested along interstitial microvascular capillaries of the lung and the damage of endothelial cells is neutrophil dependent, it is possible that in this situation PEG-derived antioxidant enzymes have ready access to oxidant products of neutrophils, whereas in the pancreas the enzymes cannot gain sufficient access to pancreatic acinar cells, which are external to the vascular compartment. These data taken together support the hypothesis that the mediators of lung injury include H_2O_2 or H_2O_2-derived products.

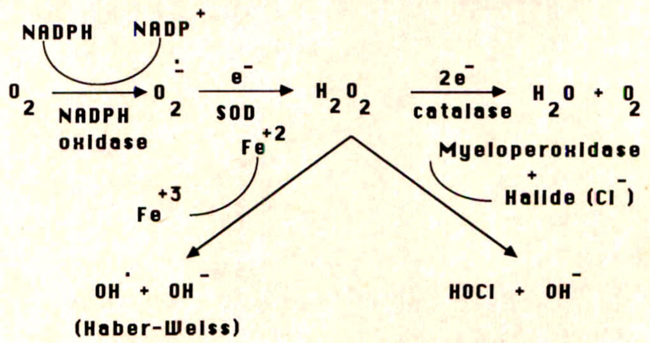


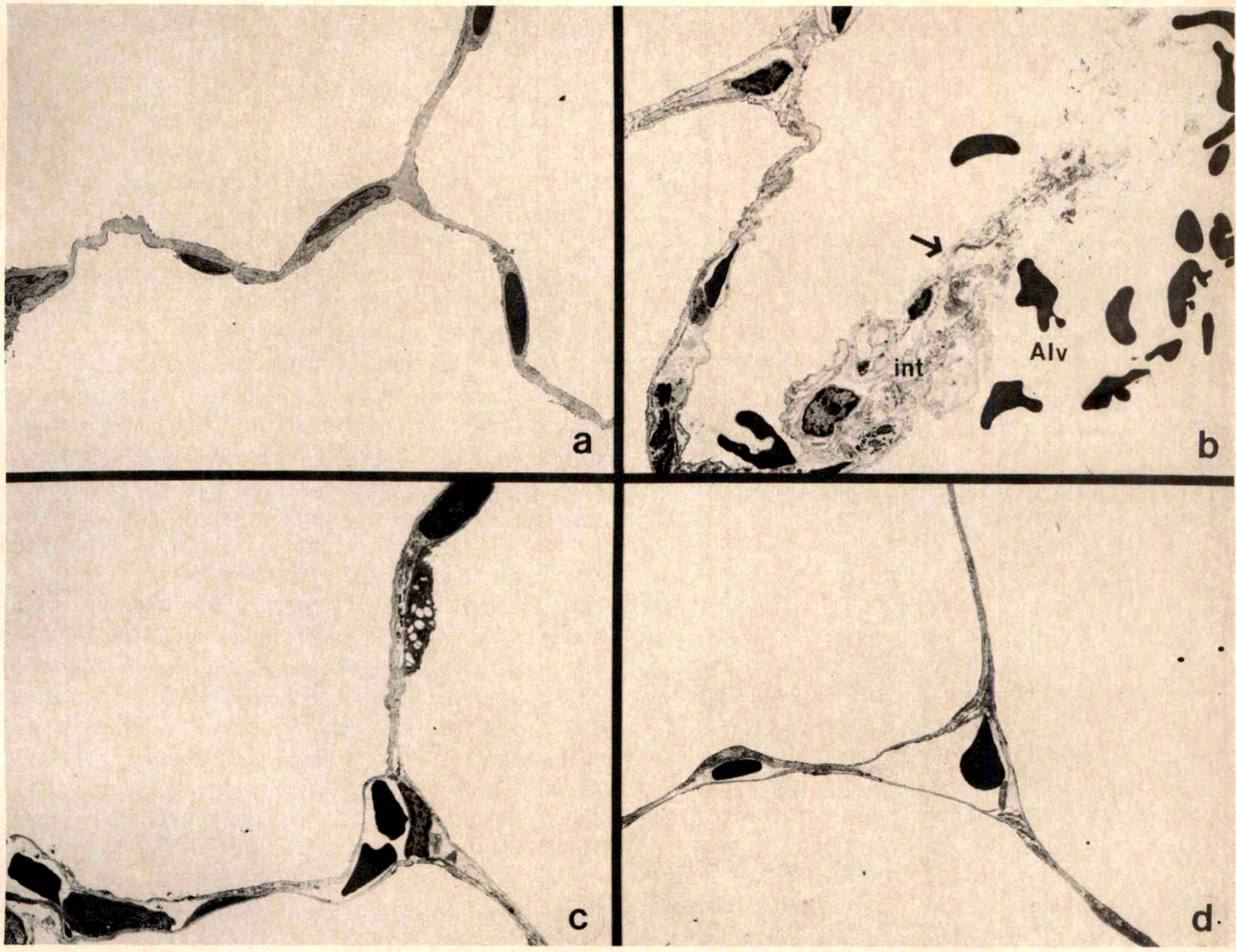
FIG. 2. The sequential reduction of molecular oxygen to H_2O_2 and ultimately $H_2O + O_2$ is illustrated together with the short-lived toxic oxygen-radical intermediates coincidently generated. Sites of action are shown for SOD, catalase, and iron. Note particularly that the hydroxyl radical ($OH^{\bullet}$) results from the iron catalyzed Haber-Weiss reaction.

Lack of Iron in Acute Lung Injury

The iron chelator deferoxamine was not protective against the development of acute lung injury or acute pancreatitis. The data in Tables 1 and 3 show that this intervention fails to prevent increased lung weight or microvascular permeability. Furthermore pancreatic edema formation (Table 2) was at least as great in animals treated with deferoxamine. That the scavenger DMSO was not protective against either pancreatitis or acute lung injury is consistent with the failure of deferoxamine to protect against injury if $OH^{\bullet}$ were involved in this type of injury. These data suggest that microvascular injury to both the pancreas as well as the lung after infusion of cerulein is dependent on H_2O_2, which is presumably derived from neutrophils activated by products of the complement system. The failure of deferoxamine and DMSO to protect implies that the oxygen-dependent species responsible for the injury could be either H_2O_2 or a product of H_2O_2 such as HOCl, which can be generated by neutrophil-derived myleoperoxidase. It is not possible to answer this question by *in vivo* interventions because there are no known methods to inactivate myeloperoxidase *in vivo.*

Morphometric Analysis

Ultrastructural features of the acute lung injury associated with pancreatitis are illustrated in Figure 3. We



FIGS. 3A–D. Photomicrographs (X2200) are shown from a normal saline-infused rat lung (A) compared to a lung from an animal with cerulein-induced pancreatitis (B). (C) and (D) are lung samples taken from rats with cerulein-induced pancreatitis treated with SOD or neutrophil depletion, respectively. Extensive endothelial damage is present in the cerulein-infused rat lung (B, arrow), as well as intra-alveolar hemorrhage (B, Alv), and interstitial edema (B, int). These features of injury are absent in the SOD-treated, neutrophil-depleted, and normal lungs (C, D, A).

Similar attenuation of the injury was found in the other antioxidant-treated animals and complement-depleted animals, but not in deferoxamine- or DMSO-treated groups.

have previously described in nonprotected rats the features in lung of interstitial edema formation, capillary endothelial-cell injury, neutrophil sequestration, and intra-alveolar hemorrhage and fibrin deposition after cerulein-induced pancreatitis.[4] Representative photomicrographs in the neutrophil-depleted and SOD-treated animals show protection against edema formation and capillary endothelial-cell injury. Similar findings of an attenuated injury were obtained in PEG-SOD-, CAT-, and PEG-CAT-treated, and complement-depleted animals. Except in those animals that were depleted of circulating neutrophils, neutrophil sequestration in the alveolar capillaries occurred even in animals that were subjects of protective interventions (Table 4). These findings are consistent with the hypothesis that neutrophil recruitment and adherence to alveolar capillary endothelial cells occurs initially, followed by the *in situ* generation of toxic oxygen products.

Discussion

Acute lung injury associated with acute pancreatitis is a common feature of human disease and can be reproduced experimentally in rats with cerulein-induced pancreatitis. The lung injury shares some clinical and histologic features of ARDS and is believed to result, in part, from activation of the endogenous inflammatory response.[4] The experiments presented above use techniques of neutrophil depletion, complement depletion, and antioxidant treatment to examine the mechanisms by which pancreatitis-induced lung injury occurs.

TABLE 4. *Lung Morphometric Analysis of Rats with Acute Lung Injury Associated with Cerulein-Induced Pancreatitis*

Intervention	PMN/HPF	n
Saline controls	0.83 ± 0.13†	60
None	6.65 ± 0.53*	60
SOD	4.74 ± 0.74*†	38
PEG-SOD	2.75 ± 0.97*†	105
CAT	3.86 ± 0.69*†	52
PEG-CAT	3.59 ± 0.53*†	59
Complement depleted	1.60 ± 0.62†	57
Neutrophil depleted	<0.1	45
Deferoxamine	4.80 ± 0.48*†	68

PMN/HPF, mean number of PMNs observed in 40× high-power field on 1 micron toluidine blue sections (normalized as experimental minus paired saline-infused control values).

n, = number of high power fields counted (40×).

* $p < 0.05$, comparing cerulein-treated animals to saline-infused controls. (Student's t test).

† $p < 0.05$, comparing experimental groups to groups with cerulein-induced pancreatitis and no intervention (None) (Student's t test).

SOD, superoxide dismutase.

PEG-SOD, polyethylene glycol SOD.

CAT, catalase.

PEG-CAT, PEG catalase.

Depletion of circulating neutrophils protects against the development of pancreatitis-induced lung injury using histologic criteria, lung weights, and ^{125}I extravasation as an index of lung microvascular permeability. Using similar end points, depletion of complement before the induction of acute pancreatitis prevents development of lung injury. Both complement and neutrophil depletion diminish the magnitude of pancreatic edema formation in ceruelin- infused animals, however significant edema formation still occurs. In addition acinar-cell injury, qualitatively estimated by enzyme (amylase and lipase) release, is not attenuated by neutrophil or complement depletion. Because a pancreatic injury is induced in these experiments but the lung injury is prevented, a role for complement products and neutrophils is inferred in the pathogenesis of the lung injury. Similarly catalase infusion protects against lung injury and attenuates pancreatic edema formation but not acinar-cell enzyme release. This suggests that H_2O_2 or its derivatives are involved in the development of this lung injury.

Treatments with antioxidant enzymes SOD, PEG-SOD, and PEG-CAT are also protective against lung injury, supporting the concept of a phlogistic role for H_2O_2 or its derivatives. The iron chelator deferoxamine is not protective nor is the hydroxyl radical scavenger DMSO. These data would tend to preclude a role for the hydroxyl radical. It is possible that myeloperoxidase-generated products from H_2O_2, such as hypochlorous acid, may be the key toxic oxygen products.

These data are consistent with the hypothesis that complement- activated neutrophils and the oxygen radicals generated by these neutrophils are important mediators of the pulmonary capillary injury. A pattern consistent with other types of experimental lung injury includes the generation of the complement activation product, C5a, which both activates and recruits neutrophils to sites of inflammation. Activated neutrophils adhere to alveolar capillary endothelial cells and generate oxygen-radical species including the superoxide anion and H_2O_2 derivatives such as the hypohalous acids.[19] Evidence for an active role of target endothelial cells has also been recently provided.[20] Neutrophil-derived oxygen radicals are known to be capable of endothelial-cell injury and killing *in vitro* and are believed to have similar potential *in vivo*.[19] This concept is supported by the observation that by blocking any one of three elements the complement system, neutrophils, or oxygen-radical formation protects against pancreatitis-induced acute lung injury. This proposed sequence is summarized diagrammatically in Figure 4.

The acute lung injury associated with cerulein-induced pancreatitis in rats appears to be complement, neutrophil, and oxygen-radical dependent. The events related to the process of complement activation and the inflammatory response within the pancreas are yet to be determined.

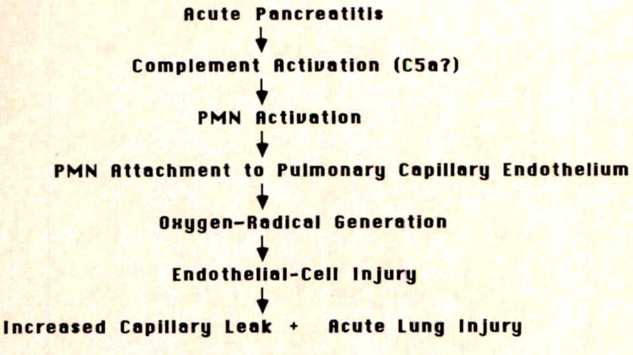

Acute Pancreatitis
Complement Activation (C5a?)
PMN Activation
PMN Attachment to Pulmonary Capillary Endothelium
Oxygen-Radical Generation
Endothelial-Cell Injury
Increased Capillary Leak + Acute Lung Injury

FIG. 4. Proposed sequence of pathogenic events in the development of pancreatitis-induced acute lung injury.

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Hepatectomy Without Abdominal Drainage

Results of a Prospective Study in 61 Patients

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The increasingly simple postoperative course of major surgery has challenged the routine use of drainage after most abdominal surgical procedures. Therefore a prospective study was designed to determine if abdominal drainage could be safely avoided after liver resection and was evaluated in 61 consecutive patients. There was one postoperative death (1.7%) from variceal bleeding. Four other patients (6.7%) developed an abdominal complication: two right subphrenic hematomas requiring reoperation in one case and two incisional ascitic leaks requiring incisional repair in one patient. There was neither a subphrenic abscess nor bile peritonitis. Postoperative hospitalization was 11.5 ± 3 days in the entire group and 8.5 ± 1 days in patients without complications. These results suggest that liver resection can be performed safely without abdominal drainage and that the routine use of drains is unnecessary.

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DURING THE LAST DECADE, progress in surgical technique and technology has made abdominal surgical procedures safer with a lower rate of postoperative complications and has simplified postoperative care. Abdominal drainage, which once was considered obligatory whenever the peritoneum had been opened, is now used, particularly as a routine, less and less when the surgical procedure has been satisfactory.[1] Drainage is not completely without its complications[2] such as ascending infection[3] and vascular[1] or intestinal ulceration.[4] The presence of a drain usually increases the nursing acuity[5] and prolongs the need for postoperative nursing care and hospitalization.[6] Finally it is uncomfortable and unpleasant for patients.[5] After cholecystectomy,[5,7-10] splenectomy,[11] or colectomy,[12] patients fare as well or even better without drains. However drainage is still regarded as indispensable after liver resection[13-15] based on the high risk of postoperative bleeding, bile leakage, and fluid accumulation in the space left empty by removal of liver parenchyma.

Because our postoperative local complication rate was low after liver surgery,[16] we started, in June 1985, a staged prospective study of the elimination of abdominal drainage after hepatectomy. This was first applied to patients undergoing a limited liver resection and following good results to two groups undergoing major liver surgery. The purpose of this work is to report the results of this policy of avoiding drainage in 61 consecutive liver resections.

Patients and Methods

From June 1985 to November 1988, 61 patients had liver resection without abdominal drainage. There were 34 men and 27 women averaging 54 years (range, 20 to 81 years). The indications for liver resection are given in Table 1. Hepatocellular carcinoma was the most common indication. Twenty-five patients had liver cirrhosis.

The type of resection was according to the liver anatomy of Couinaud[17] and is indicated in Table 2. There were 26 major resections, 18 segmentectomies, and 17 nonanatomic liver resections. Most of the latter were performed in patients with cirrhosis.

Resections were performed as previously described.[16] All operations were done through a long subcostal incision. Liver transection was done by kelly fracture. Hemostasis and bilistasis of any single radicle was done by resorbable clips (Ethicon^R, Neuilly Sur Seine, France). Ultrasonic or microwave dissectors were not used. Temporary clamping of the hepatic pedicle was used in 40 patients for a mean period of 25 minutes (range, 20 to 57 minutes) to avoid excess bleeding. Normovolemic he-

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TABLE 1. *Indications for Liver Resection in 61 Patients*

Indication		n
Hepatocellular carcinoma		27
With a normal liver	2	
With a cirrhotic liver	25	
Liver metastases		16
From a colorectal cancer	10	
From another primary cancer	6	
Benign liver tumors		13
Cholangiocellular carcinoma		3
Intrahepatic cholelithiasis		2

modilution was used in 19 patients to decrease blood transfusions. All resections evolved without intraoperative complications. Mean operative duration was 240 ± 80 minutes, mean blood transfusion was 3 ± 2 units of packed red cells, and mean infusion of fresh frozen plasma was 4 ± 3 units.

A prospective study on the suppression of abdominal drainage was assessed in three successive groups of patients: 15 patients with a normal liver and limited (segmental or nonanatomic) resection, starting in June 1985; 20 patients with a cirrhotic liver and a limited resection, starting in May 1986; and 26 patients with a major hepatectomy and a normal or cirrhotic liver starting in January 1988. No patient had abdominal drainage once the protocol was begun in any of these three groups.

Before closing the abdomen, hemostasis and bilistasis of the transection plane were carefully checked and completed when necessary. No surgical glue was used. After left liver resection, the empty space was easily filled by the stomach, colon, and great omentum. After right hepatectomy the greater omentum was mobilized and, when necessary, the hepatic flexure was released to fill the right subphrenic space. The abdomen was closed in three layers by resorbable running sutures.

Cirrhotic patients received a short (one-day) perioperative course of cefotetan (1 g twice) and patients with a normal liver had no prophylactic antibiotherapy.

Results

One cirrhotic patient (1.7%) died four days after resection of segment IV from variceal hemorrhage. There were no abdominal complications at autopsy. The following results are given on the 60 survivors.

Fourteen complications (23.3%) occurred in 13 patients (21.7%). They are summarized in Table 3. There were four abdominal complications (6.7%). Two patients had a right subphrenic hematoma. The first occurred after segmentectomy V in a patient with a normal liver and a benign tumor. It was triggered by use of low-molecular-weight heparin on trial and was treated by percutaneous drainage. The second occurred after a right hepatectomy for hepatocellular carcinoma in a cirrhotic patient and required reoperation. No precise site of bleeding was found and the recovery was uneventful. Two other patients had an ascitic leak through the wound. The first occurred after resection of segment VIII for a hepatocellular carcinoma in a cirrhotic patient with chronic respiratory failure. Strenuous coughing at extubation resulted in a small incisional dehiscence and leak of ascites that required repair. The last patient developed neoplastic ascites ten days after an extended right hepatectomy for a bulky cholangiocarcinoma, resulting in a self-limited ascitic leak through the incision.

TABLE 2. *Type of Liver Resection in 61 Patients*

Resection	Patients with a Normal Liver	Patients with a Cirrhotic Liver	Total Number
Major liver resections	21	5	26
Right hepatectomy	17*	3	20
Left hepatectomy	4†	2	6
Segmentectomies	8	10	18
One segment	2	8	10
Two segments	6	2	8
Nonanatomic liver resections	7	10	17

* Four patients had a right hepatectomy extended to segment IV.
† Two patients had a left hepatectomy extended to segment V.

All other complications were benign. Among seven patients with right pleural effusions, three had asymptomatic subphrenic fluid collection at ultrasonographic examination, all of which subsequently disappeared.

The rate of abdominal complications was similar after major hepatectomies (7.7%) and limited liver resections (5.9%). Abdominal and general complications were slightly higher but not significantly so in cirrhotic patients (8% and 28%, respectively) compared to patients with a normal liver (5.7% and 20%, respectively).

The mean postoperative hospital stay was 11.5 ± 3.6 days. It was 18 ± 9 days in the 13 patients with complications and 8.5 ± 1 days in the 47 patients with no complications.

Discussion

These results suggest that liver resection can be performed safely without abdominal drainage.

The imperative need for liver drainage was based on a high rate of postoperative abdominal complications in earlier series of liver resections, including postoperative

TABLE 3. *Complications After Liver Resection in 61 Patients*

Subphrenic hematoma	2*
Wound ascitic leak	2†
Right pleural effusion	7
Ascites requiring peritoneal tap	1
Incisional abcess	1
Pneumonia	1

* One patient required reoperation in the 12th postoperative hour.
† Incision was reclosed on the 6th postoperative day.

bleeding, biliary fistulas, and subphrenic abscesses.[13,14,18] Bleeding and bile leaks from the transection plane, together with remnants of devitalized liver tissue, were key factors in the origin of complications.[15] However progress in liver surgery technique has decreased the frequency of postoperative complications.[16,19] In a series of 100 consecutive liver resections for tumor, there were 1 subphrenic abscess; 1 biliary fistula resulting from accidental severance of a major bile duct, and 3 subphrenic hematomas.[16] Gentle transection of liver parenchyma along anatomical planes by kelly fracture and the use of surgical clips, which allowed careful closure of any small vascular and biliary radicles, determined this low incidence of postoperative complications.[16]

In the present series, only four (6.7%) postoperative abdominal complications occurred. Of these only the ascitic leaks might have been prevented or controlled by drainage. However they were minimal and easily managed in both patients. The diagnosis of right subphrenic hematoma was easily done, despite the absence of drainage, by ultrasonography. Fluid accumulation in an empty space after abdominal surgery is a natural event and it has been suggested that drains increase the amount of serous fluid.[20,21] In our patients asymptomatic fluid collections were eventually discovered by ultrasonographic examination in three patients with right pleural effusion. Interestingly none became infected and they vanished without treatment.

The risk of ascending infection along abdominal drains has already been emphasized[3] and it appears that after surgery for liver trauma infectious complications are less frequent when drainage was not used.[22-25] In 17 cirrhotic patients undergoing liver resection with closed abdominal drainage, postoperative infection of ascites occurred in four,[26] a complication that has not occurred since we stopped using drains.

None of the patients had bile peritonitis. Previous data suggest that after hepatectomy significant bile leaks result from injury to a major bile duct.[14] This is also the case in our experience.[16] Minor bile leakage from the transection plane is reabsorbed.

Elimination of abdominal drainage decreases postoperative patient discomfort,[6,10] simplifies the postoperative course, and shortens hospitalization.[5,6] In our early experience following hepatectomy in cirrhotic patients, a prolonged flow of fluid through abdominal drains was responsible for delayed postoperative hospitalization that averaged 17 days and significant infectious morbidity.[16,26] When elimination of drainage was found safe for limited resections, it was tried in cirrhotics and eliminated the infectious complications and reduced postoperative hospitalization by almost 50%.[26] In addition to the advantages for patients, this has markedly decreased the cost of liver surgery. When forgoing drainage was safe in cirrhotics, the concept seemed appropriate in all hepatic resections unless there was a compelling reason to drain.

These data support the concept that abdominal drainage need not be used routinely after liver resection. It is noteworthy that since January 1988, when all patients were entered into this study, drainage has not been used for any patient, regardless of the liver resection.

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Carcinoma of the Gallbladder

The Roswell Park Experience

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The median survival, from diagnosis, of patients with cancer of the gallbladder is 6 months. Our purpose in reviewing our experience was to identify factors, either in patient characteristics or treatment, that influence this statistic. In 22 years 71 cases of gallbladder carcinoma were referred to Roswell Park Memorial Institute in Buffalo, New York. Most had a cholecystectomy that revealed an unsuspected neoplasm, before referral. Mean age was 62 years and 75% were female. Symptoms, signs, and laboratory and imaging studies were uniformly unhelpful in determining the diagnosis. Early diagnosis at a stage amenable to surgical excision remains the sole salvation. Patients who receive chemotherapy did better than those who did not, but this is probably a reflection of patient selection. Newer treatment modalities are urgently needed.

CARCINOMA OF THE gallbladder is the fifth most common tumor of the gastrointestinal tract.[1] Approximately 6600 new cases are diagnosed each year in the United States, and this figure is matched by an almost equal number of deaths.[2] Most occur in the cancer age group, peaking in the seventh decade, with women affected three times as commonly as men.

Although first described by Maximillian deStoll in 1777,[3] the prognosis for patients with this disease is still dismal. The overall 5-year survival rate is less than 5%.[4] Diagnosis is most commonly made at time of laparotomy for presumed cholecystitis. Seventy per cent of the cases are unresectable.[5] Radical surgery fails to improve cure rates, even in those cases deemed suitable for it. Only in those patients in whom the tumor is first diagnosed by the surgeon or the pathologist, when examining the resected gallbladder and is found not to penetrate the serosa, is cure likely. Simple cholcystectomy can be the curative procedure,[6] but a wedge excision of the gallbladder bed off the liver and a portal lymphadenectomy is advised.[7] There is little evidence that more extensive procedures significantly increase survival rates.[1] The role of radiation therapy and chemotherapy is not yet defined, but experience, until now, has been disappointing.

Because of the uniformly poor experience reported in the literature, we have reviewed our results to see if we have been any more efficacious in our attempts at attacking this disease and identifying any factors of prognostic or therapeutic significance.

Materials and Methods

The records of 71 patients with histologically proved carcinoma of the gallbladder seen at Roswell Park Memorial Institute (RPMI) between 1964 and 1986, were reviewed. Patient age and sex, presenting symptoms and signs, and the technique for establishing the diagnosis were noted. The stage of disease at the time of diagnosis was compared to the duration of symptoms. Surgical procedures and other therapies were reviewed with regard to their effect on survival. Analysis of autopsy data permitted evaluation of the effect of treatment on dissemination of the cancer.

Results

At the time of presentation to RPMI, the mean age of the patients was 62.1 years, with a range of 36 to 48 years. Eighty-three per cent were older than 50 years. Seventeen (24%) of the patients were male, and 54 (76%) were female. Sixty-seven (94%) of the patients had adenocarcinoma,

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and four (6%) had squamous cell carcinoma. The sites of tumor spread were evaluated in the 52 patients with advanced disease. Invasion or metastases to the liver substance was found in 42 patients. Cystic duct, common bile duct, and peripancreatic lymph nodes were the seat of metastases in 22 patients. Diffuse carcinomatosis was seen in 17 patients. Other sites of tumor spread included the surface of the colon (two patients), the omentum, pancreas, abdominal wall, and the substance of the lung (one patient each).

In all 71 patients confirmation of the diagnosis was made by review of the histopathologic materials or at autopsy.

The stage of disease used was based on a classification by Moran and Nevin.[8] Stage I: disease localized to the mucosa; stage II: tumors that penetrate the muscularis; stage III - tumors that involve all three layers; stage IV: metastases in the cystic duct lymph nodes; and stage V: invasion or metastases to liver or to adjacent or distant organs.

Fifty-two patients had stage V disease when they were first seen at RPMI, most of whom had already been found to have advanced disease at the time of exploration before referral to RPMI (Table 1). A few were referred some months later when symptoms indicated the inexorable spread of their disease.

In none of the 71 patients had the diagnosis been made before operation. In seven (10%) the diagnosis was first made at autopsy. All these had stage V disease. In 35 patients (50%), diagnosis was made by the surgeon, whereas in 29 (40%), the diagnosis was not made until the pathologist examined the specimen. Except in the cases of stage II and III disease, the difficulty was not in the diagnosis of cancer, but in determining the site of origin. Thus the fact that diagnosis was unavailable until histopathologic review did not affect outcome.

Information with regard to the duration of symptoms before diagnosis was available in 62 patients. While there were no identifiable symptoms in one patient, symptoms were present for more than 10 years in another. Median duration was 1.8 months. The most common symptoms were pain (55 patients), nausea (32 patients), vomiting (25 patients), jaundice (25 patients), and weight loss (20 patients). Only three patients had, as an initial complaint, a mass in the abdomen. One patient developed a nonhealing ulcer in the abdominal wall at the site of a previous cholecystostomy, which contained metastatic tumor.

TABLE 1. *Stage of Disease at Referral*

Stage	Number of Patients
II	2
III	7
IV	10
V	52

When referred to RPMI, serum bilirubin was elevated in only 26 patients, despite the late stage of disease. The median bilirubin was 0.8 mg/dL and ranged from 0.3 to 27.0 mg/dL. Alkaline phosphatase was elevated in 54 patients. The mean and median values were approximately four and two times the upper limits of normal, respectively. Albumin levels ranged from 1.2 to 5.3 gm/dL, with a mean and median of 3.4 gm/dL. Abnormal aspartate amino transferase levels were found in 41 patients, and the mean and median values were 2 and 1.5 times above normal.

Radiologic investigations performed varied and were nondiagnostic. The most common finding was a nonspecific nonvisualization of the gallbladder. Cholelithiasis was present in 48 patients (68%) but was absent in 21. In two cases the records from referring hospitals did not mention the presence or absence of stones. A calcified ("porcelain") gallbladder, a highly predisposing condition, was found in seven patients (10%).

Acute or chronic cholecystitis was noted in the pathologic examination of 54 gallbladders, but in 15 patients there were no signs of inflammation. For the remaining two patients this information was unavailable. Diabetes was present in 6 patients (8.5%). Obesity and alcoholism were not found to be associated with this malignancy.

A second cancer was present, or had been present, in nine patients (13%). In one patient autopsied after death from adrenocortical carcinoma, the gallbladder cancer was an incidental finding. Another patient, apparently cured by cholecystectomy, died of metastatic breast carcinoma years later. Other carcinomas occurring in patients with gallbladder cancer included prostate, colon, and skin.

Initial treatment usually consisted of a cholecystectomy (47 patients). In 18 of these patients a common bile duct exploration had been performed as well (Table 2). Most of the surgical procedures performed after referral to RPMI were of a palliative nature. Even when the intent was curative, survival was not markedly prolonged. The two patients who underwent a right hepatic lobectomy survived less than 6 months.

Chemotherapy was administered to 62% of the patients (Table 3). The most commonly used agents included 5-fluorouracil, methotrexate, etoposide, cis-platin, doxorubricin, and methyl-CCNU, alone or in combination. Drug combinations were more common in the later years of the study. Seventeen patients received radiation dosages ranging from 11 to 70 Gy, often in combination with 5-fluorouracil.

The survival of patients who received chemotherapy was somewhat longer than that of patients who did not receive these agents. Because of uncontrolled variables (such as radiation therapy) and the diversity of the treat-

TABLE 2. *Surgical Procedures*

Operation	Stage II–III	Stage IV	Stage V
Cholecystectomy	9	7	31
Plus CBDE	3	4	11
Plus gastrojejunostomy			8
Hepaticojejunostomy	2	2	9
Exploratory laparotomy above	0	1	11
Cholecystojejunostomy*	0	1	0
Choledochoduodenostomy	3	0	2
Choledochojejunostomy	0	0	1
Right hepatic lobectomy	0	0	2
U tube insertion	2	0	1
Right hepatic artery ligation	0	1	0
Total patients	9†	10	52

Note, one patient (*) revised at Roswell Park Memorial Institute to Cholecystectomy and Hepaticojejunostomy. Only two patients (†) had stage II disease.

TABLE 4. *Possible Benefit of Chemotherapy on Survival*

Treatment	Number	Survival
Chemotherapy	41	8.4 months
No Chemotherapy	23	5.3 months

Seven patients who were diagnosed at autopsy are excluded.

ment regimens used, there is no more than a vague suggestion that chemotherapy may have been the common denominator in prolonging survival (Table 4).

The length of survival was calculated from the date of onset of symptoms and from the date of diagnosis in 62 patients (Table 5, Figs. 1 and 2). In seven patients, diagnosis was made at autopsy; in two others complete information was not available. Comparing survival to the stage of disease at diagnosis demonstrates the expected correlation, at least during the first year. Median survivals for stages II to V are listed in Table 6. Stage of disease was the only factor identified that consistantly influenced survival. Four patients are alive at 14.5, 18, 21, and 36 months.

Discussion

Carcinoma of the gallbladder is the most common malignancy of the biliary tract, comprising two thirds of biliary-tract cancers. It is the fifth most common cancer of the gastrointestinal tract.[1] Advances made in the management of other gastrointestinal tumors have not extended to gallbladder cancer. Early diagnosis and late palliation are difficult.

The autopsy incidence of this malignancy varies from 0.18% to 0.81%, with little evidence of change during four decades. In 1949 Arminski noted a malignancy rate of 0.43%.[9] The incidence of gallbladder cancer in the United States has been calculated by Burdette to be 2.5 per 100,000 inhabitants.[10] Among patients undergoing surgery for biliary-tract disease, cancer has been found in 1% to 2%,[10,11] with the frequency of gallbladder cancer peaking in the seventh decade of life.[5,12–14] However carcinoma of the gallbladder has been recorded in an 11-year-old child. A preponderance of female patients (75% in this series) has been noted previously[9,15,16] and may suggest an association between benign and malignant gallbladder disease.

Cholelithiasis was present in 68% of the patients in the present series. Strauch reported that 54% of patients had gallstones, but excluded 37% of the patients studied whose gallbladders had not been examined for stones.[15] Piehler reviewed 37 series and reported an average incidence of 74%.[16] Warren and Balch demonstrated a greater incidence of stones in patients with gallbladder cancer than in age-matched controls.[17] In this series the incidence of gallstones in male and female cancer patients was the same. However stones cannot be the only causative factor because one third of patients who have cancer do not have associated gallstones. Autopsy studies indicate that only 1% to 3% of patients with cholelithiasis develop this cancer. In a 10-to-25-year follow-up of patients with asymptomatic gallstones, Comfort et al.[18] found fewer than 1% of patients developed cancer.

Chronic irritation in areas such as the bronchus and cervix are associated with metaplasia of the columnar

TABLE 3. *Patients Treated with Chemotherapy and Radiation Therapy for Gallbladder Cancer*

Stage	Patients (total)	Chemotherapy Alone (n)	Radiation Therapy Alone (n)	Both Modalities (n)
II	2	2		
III	7	3	2	1
IV	10	3	1	1
V	52	24	4	10

* These patients were treated when they were later found to have recurrence.

TABLE 5. *Survival Data for Patients with Gallbladder Cancer*

Survival	Survival from Symptom Onset	Survival from Diagnosis
Median survival	8 months (0.8–131+ months)	6.6 months (0–124.3 months)
Estimated 2-year survival	20%	10%
Estimated 5-year survival	9%	3%

* Seven patients were diagnosed at autopsy and are omitted from this table. Complete information was not available in 2 other patients.

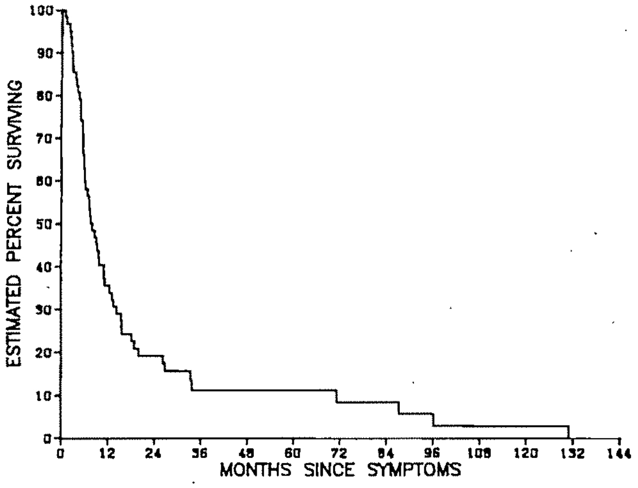

FIG. 1. Estimated survival from onset of symptoms.

TABLE 6. *Survival Based on Stage*

Stage	Number of Patients	Median Survival (months)
II	2	24
III	7	13
IV	10	5.3
V	52	5.9

mucosa and frequently the ultimate development of squamous-cell carcinoma.[19] Considering the fact that most gallbladder malignancies are adenocarcinomas (and those that are squamous are most often proven to originate from adenocarcinomas),[20,21] the role of calculi and inflammation in the causation of this disease must be seriously questioned.

Cholecystitis and calcified ("porcelain") gallbladders have been considered to be contributing factors in this disease. In our series acute and/or chronic cholecystitis was present in 54 cases (76%), and a calcified gallbladder was found in seven (10%). Because patients with "porcelain" gallbladders also had gallstones, it is difficult to attribute an exact role to each of these factors.

The overall increased frequency of gallbladder cancer in women and bile duct cancer in men suggests that hormonal factors play a role. Among African Bantus, cholelithiasis and gallbladder cancer are both very rare, while in Southwestern American Indians the incidence of both is high. Population differences such as these[12] suggest a possible genetic susceptibility.

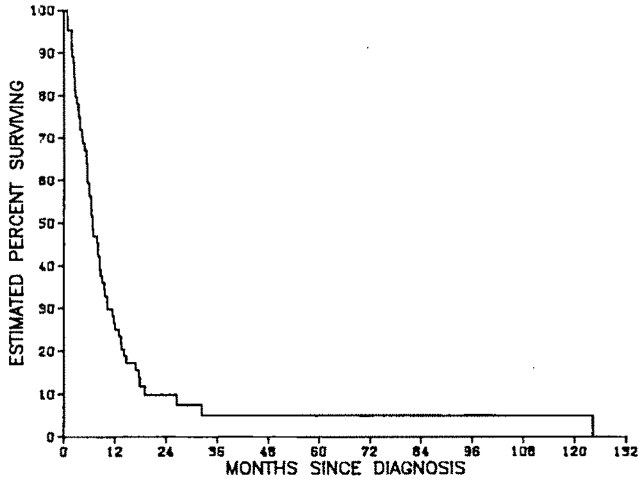

FIG. 2. Estimated survival from onset of diagnosis.

Chemical carcinogens, especially nitrosamines and methylcholanthrene, have been implicated in the etiology of gallbladder cancer.[22] Laboratory studies have suggested a multifactorial etiology, where gallstones, inflammatory processes, and chemical carcinogens all play roles of inducers and facilitators.[23]

Benign gallbladder tumors do not seem to be precursor lesions for gallbladder carcinoma. Strauch found only one case of carcinoma *in situ* arising in an adenomatous gallbladder polyp.[15] A similar case was reported by Glenn.[24]

While ulcerative colitis has been shown to be associated with cancers of the extrahepatic ducts, the incidence of carcinoma of the biliary tract being five to ten times more common in patients with ulcerative colitis than in the general population,[25] only 13% of these biliary-tract cancers originated in the gallbladder.

Clinical diagnosis of gallbladder cancer is a difficult task. In some patients the only complaints that suggest malignant disease are weight loss and anorexia. Others may present with a complication such as gastrointestinal hemorrhage, which obscures the primary problem. Even in the common situation in which symptoms and signs relate to the biliary tree, the similarities between carcinoma and benign disease make the diagnosis difficult.

Serum chemistries have not been helpful because the serum bilirubin is often normal. Chemical jaundice was present in only 26 patients (36%) in our series. Our experience confirms that of Vaittinen[26]: elevated alkaline phosphatase levels often accompany normal serum bilirubins in this disease.

One might be more suspicious of neoplasia when the abdominal roentgenograms show a calcified gallbladder.[4] Oral cholecystography, except in anecdotal instances, has been useless. Intravenous or percutaneous cholangiograms are not much better. An upper gastrointestinal contrast study may show displacement of stomach and duodenum when extensive disease is present, but the findings are not specific. Computerized tomography and ultrasonography can aid by the identification of an irregular thickening of the gallbladder wall. Angiography, demonstrating irregularities and tumor vessels arising from the cystic artery, is not a screening procedure. By the time diagnostic changes are present, the tumor is incurable. Duodenal aspirations and peritoneoscopy have not been helpful as screening procedures either.

In Strauch's series, the preoperative diagnosis was correct in 13% of cases.[15] A review by Piehler reported an average frequency for correct diagnosis of 9%.[16] The present report notes that in no instance was diagnosis made before operation.

It has been suggested that gallbladder cancer evolves from hyperplasia to atypia, to carcinoma *in situ*, and frank carcinoma. Albores-Saavedra et al.[27] reported that 83% of gallbladders with stones or inflammation showed hyperplasia and 13.5% showed atypical epithelial changes. In patients with carcinoma *in situ*, atypical hyperplasia was found nearby. A 5-year difference in the mean ages of patients with carcinoma *in situ* and atypical hyperplasia was noted. This age difference strengthens the argument for this proposed progression.

Gallbladder cancer can be found as a polypoid projection into the lumen of the gallbladder (the type most often reported as an incidental finding) or as a diffuse thickening of the wall of the organ, with or without extension into the liver and other adjacent organs. In our series, the liver and the regional lymph nodes were involved by cancer in 42 (59%) and 22 (31%) of patients, respectively. The next most common manifestation of spread was peritoneal carcinomatosis (18 patients, 25%), which occurred more often than had been expected.

The histopathologic types of gallbladder cancer, as noted by Piehler and Crichlow,[16] include adenocarcinoma, squamous-cell carcinoma, undifferentiated carcinoma, adenoacanthoma, carcinoma *in situ*, mixed malignant lesions of epithelial origin (carcinoid and melanoma), and mesodermal lesions (rhabdomyosarcoma, fibrosarcoma, leiomyosarcoma, and lymphoma). Adenocarcinomas are, by far, the most common (82%), as also noted in our series (67 patients, 94%). The four squamous-cell cancers (6%) represented the only other histology seen in this series. In the southwestern United States, squamous tumors are more common among the Native American population, a squamous component having been noted in 35%.[12] No age predilection for the various histologic types has been reported.

Spread of epithelial tumors is by local invasion and through lymphatics of the biliary tree, regardless of tumor histology. Direct communication to the subcapsular lymphatic channels in the liver do exist and serve as an additional route of dissemination.

Cholecystectomy alone is generally effective in those cases in which the carcinoma is an incidental finding on histopathologic examination of a gallbladder removed for symptomatic benign disease.[28] Shieh reported a 66.6% 5-year survival for patients whose tumors were confined in the wall of the gallbladder and were found incidentally by the examining pathologist.[5] However the lesion is generally incurable when the cancer has invaded to the gallbladder serosa.

There have been few instances in which cancer diagnosed at laparotomy led to a successful resection. Approximately 15% of patients can be made grossly free of disease by resections, including a wedge of adjacent liver, combined with hepatic and periportal lymphadenectomy, the procedure advised by Glenn and Hays,[24] and by Warren and Camer.[29] In the review of patients seen at the Mayo Clinic between 1960 and 1972, only 9 of 26 with theoretically resectable gallbladder cancers with full-thickness wall penetration and either liver invasion or regional lymph node metastases were treated by wedge resection of the liver and lymph node dissection. Of the six patients who actually did have local spread of disease beyond the gallbladder, two survived more than 5 years.[7]

The two patients in our series who underwent a right hepatic lobectomy survived for less than 6 months. Another patient treated by right hepatic artery ligation also survived for 6 months. In the face of more extensive disease, aggressive surgery does not seem to prolong life.

Proponents for more radical procedures, such as right hepatic lobectomies, have reported occasional 5-year survivors,[30] but the morbidity rate makes it difficult to wholeheartedly endorse these suggestions. At the opposite extreme a somewhat larger group of surgeons believe that carcinoma of the gallbladder is not a surgical disease. It is difficult to find sufficient proof to convince the latter otherwise.

One major management question that arises with unfortunate frequency is that of the patient whose cancer is found in the specimen by the pathologist one to two days after cholecystectomy. If the tumor is confined to the gallbladder wall, reresection probably offers no advantage (and considerable risk of complication) compared to the operation already performed. For patients in whom the tumor extends through the gallbladder wall, reresection offers little, as the literature records only two patients who had long-term survival after a reresection that demonstrated residual cancer.[31,32]

A benefical effect of chemotherapy or radiation has yet to be demonstrated. Anecdotal reports of responses, with slight prolongation of survival for patients who receive combined modality therapies, encourage further trials in defined populations, but the evidence is too weak to be the basis for treatment recommendations outside of clinical trials. In this study, benefit may represent selection of patients whose performance status, survival, and clinical chemistries would permit them to receive the chemotherapy in the first place. Of patients with inoperable gallbladder cancer, the Eastern Cooperative Oncology Group reported that only 5 of 53 patients (less than 10%) responded. Survivals of 5, 7, 11, 15, and 57 weeks in responding patients, balanced by the toxicity of these programs, suggested to the authors of the study that these chemotherapy regimens did not warrant further study.[33] Newer drugs and alternate routes of delivery are essential if there is to be any success with this line of treatment.

The small numbers of patients seen at any individual institution make evaluation of any form of therapy for this disease difficult. If all patients diagnosed to have gallbladder cancer entered into cooperative trials, more helpful information might be obtained. While radiation therapy has been advocated for squamous-cell cancers,[10] one might wonder whether even a cooperative trial might determine the value of this recommendation because of the even smaller number of patients with this pathologic diagnosis.

Estimated 5-year survival in this series from the time of diagnosis is less than 3%, not very different from reported overall survival in other series.[4] Median survival in the current series of 6.4 months is little different from the experience in New Orleans (4.1 months)[34] and at the Mayo Clinic (2.5 months).[35]

In view of the dismal outlook for this disease, prevention would be an important goal. If the presence of gallstones could be definitively established as a major factor in the etiology of this disease, removal of gallbladders containing nonsymptomatic stones would be appropriate if the risk of the operation were less than the risk of cancer (although it isn't). Prevention remains an elusive goal.

Improvement of the outcome of intermediate stages (stages II and III) of this disease might result from careful examination of the resected gallbladder in the operating room with frozen section examination of any suspicious lesions. If cancer was identified, and adequate support facilities available, wedge resection of the liver and portal lymph node dissection might improve patient survival.

For patients with localized disease, postoperative radiation therapy combined with 5FU may offer some benefit. Early trials may have not paid attention to the nutritional and performance status of patients during treatment, a factor that may explain the uniformly poor results. With emphasis being placed on nutritional support, patients tolerate more rigorous therapy, suggesting a potential for improved results. Chemotherapy administered intra-arterially and intra-peritoneally, which deliver higher drug concentrations to the site of cancer, may increase local efficacy and reduce systemic toxicity. Combinations of agents based on pharmacologic modulation are being evaluated. As is the case with other forms of malignant neoplasia, the greatest improvements will come only with earlier diagnosis.

Between 1964 and 1986, 71 patients with carcinoma of the gallbladder were referred to RPMI. This uncommon tumor was diagnosed in 0.06% of all new referrals. A majority of patients had received their initial treatment, usually cholecystectomy, before being sent.

The mean age of the patients was 62 years. Three quarters were female. The duration of symptoms that were quite often indistinguishable from those of benign disease ranged from 0 days to 126 months. Laboratory and imaging studies were uniformly unhelpful. Diagnosis was not made until autopsy in seven patients. On initial presentation to RPMI, advanced disease was seen in 73% and peritoneal carcinomatosis was seen in 20%.

While survival was longer in patients given chemotherapy, this apparent prolongation of life may well be a reflection of patient selection rather than an effect of treatment. Median duration of survival, from date of diagnosis, was 6.6 months. Only good cancer surgery and earlier diagnosis will improve outcome. Little progress has been made in the management of this neoplasm since deStoll first described it in 1777.

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Inhibition of Tumor-Cell Attachment to Extracellular Matrix as a Method for Preventing Tumor Recurrence in a Surgical Wound

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Studies with four different transplantable murine tumors demonstrated that surgical instruments contaminated by contact with a tumor mass could produce tumors in a surgical wound. Eighty-seven per cent of mice with wounds made by invisibly contaminated scissors developed tumors. Irrigation with water did not prevent tumor growth. Before spilled tumor cells can invade and grow into a recurrence in the wound site, they must first attach to underlying extracellular matrix. We have devised a simple *in vitro* assay to identify inhibitors of tumor-cell attachment to develop therapeutic compounds that can prevent tumor-cell reimplantation. Various test compounds, including proteases (trypsin and Dispase), known modulators of matrix metabolism (proline analogues, cycloheximide, heparin, cortisone, cortexolone, and heparin-steroid combinations), large molecular weight polymers (agarose, dextran, polyethylene oxide), and synthetic fibronectin peptides were tested for their ability to inhibit mouse melanoma (B16-F10) cell attachment to gelatinized dishes. Most of these compounds had little or no effect on tumor-cell adhesion when cells were plated in serum-containing medium. However we identified three compounds that inhibited tumor-cell attachment in a reversible fashion: (1) a specific inhibitor of collagen deposition (L-azetidine-2-carboxylic acid); (2) a bacterial neutral protease (Dispase); and (3) synthetic fibronectin peptides that contained the arginine-glycine-asparate (RGD) sequence that is responsible for cell binding. Dispase and the RGD-containing peptides also inhibited cell implantation and prevented tumor formation in a surgical wound. We propose that inhibitors of attachment might be used either alone or with other biologic modifiers to prohibit implantation of free tumor cells at the time of surgery and thus, to prevent local tumor recurrence.

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THERE ARE SEVERAL explanations as to why a tumor grows back after an apparently complete resection. Usually the recurrence is blamed on a nidus of disease that was not removed in the initial resection. However that explanation is not always correct. For example when carcinomatosis follows iatrogenic rupture of a cystic ovarian tumor, it is clear that local recurrence is due to implantation of cells spilled during the resection. We now present experimental evidence of another less-obvious way in which tumor cells can be spilled into the wound during a resection, that is, from surgical instruments that have been invisibly contaminated by touching the tumor mass.

Before free cells in a wound can invade and grow into a clinical recurrence, they must first attach to underlying tissue structures. Cell attachment is a dynamic process that involves specific adhesive interactions between the cells and extracellular matrix.[1,2] It may be possible to interfere with this process at the time of surgery and thereby lessen the likelihood of local recurrence. We have devised a simple *in vitro* assay for identifying molecules that block tumor-cell attachment to extracellular matrix and present several agents that inhibit the implantation of tumor cells transferred to a surgical wound by contaminated instruments.

Materials and Methods

Animals

Adult (8 to 12 weeks old) male C57 B1/6 mice were obtained from Charles River Labs (Wilmington, MA) and housed in a temperature-controlled, 12-hour light/dark cycle environment for at least seven days before performing any procedures. Procedures were performed aseptically under methoxyflurane anesthesia (Pitman-Moore Inc., Washington Crossing, NJ).

Tumors

Four different transplantable murine tumors were used: Lewis lung carcinoma, B16-F10 melanoma, Reticulum

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cell sarcoma, and MB-49 bladder carcinoma. These tumors originated in C57 B1/6 mice and were maintained in our laboratory by subcutaneous passage.

Cell Culture

The B16-F10 melanoma variant (provided by Dr. Bruce Zetter) was used for the attachment assays. These cells were grown in Dulbecco's Modified Eagles Medium (DMEM; GIBCO Laboratories, Grand Island, NY) supplemented with 10% fetal calf serum (FCS; GIBCO), 2 mM glutamine, 100 U/mL penicillin and 100 U/mL streptomycin.

Contamination of Surgical Instruments by Tumor

The tips of a pair of iris scissors were contaminated by taking two snips of a tumor (approximately 500 mm^3) growing subcutaneously on the back of one animal. These scissors were then used to create a lateral subcutaneous pocket off of a dorsal midline wound in another animal (*i.e.*, nontumor bearing). The dorsal midline wound was closed with skin clips. After each contamination, and before use in the experimental animal, the scissors were inspected to assure that there was no visible tissue on them. Scissors were carefully wiped clean with an alcohol sponge between uses on different experimental animals. The number of cells on the scissor tips after a typical contamination was determined for each tumor type by rinsing the scissor blades with 15 mL of phosphate buffered saline without calcium or magnesium (PBS; GIBCO), centrifuging this suspension, resuspending the pellet in 1 mL DMEM, and then counting the cells with a hemacytometer or a Coulter counter.

The B16 melanoma was used to determine whether irrigation of the wound with distilled water could diminish the chances of tumor growth. A lateral subcutaneous pocket was made with scissor tips that had been contaminated with tumor cells as described above. The pocket was then filled with either saline (n = 8) or distilled water (n = 10) until the liquid ran out of the wound (approximately 2 mL). The remaining fluid was then expressed and the wound closed as before.

Assay of Tumor-Cell Attachment

Assays were done in gelatinized 96-well tissue culture plates (Costar, Cambridge, MA). The plates were gelatinized in the following manner: 100 μL of 1.5% gelatin (Difco, Detroit, MI) in PBS was added to each well and incubated at 37 C for at least 24 hours. The gelatin solution was aspirated and the wells washed twice with 200 μL of PBS before use.

A dose range of test substances was diluted to two times final concentration in culture medium (DMEM containing 10% FCS) and 100 μL were added to each well. Aliquots of the B16-F10 cell suspension (10^4 cells/100 μL culture medium) were then added to each well and plates were incubated at 37 C for 4 or 16 hours. At the end of the incubation period, the medium was aspirated, each well was washed twice with 200 μL of PBS, and the number of cells that remained attached was determined using an acid phosphatase colorometric assay as previously described.[3] Briefly, 100 μL of an acid phosphatase reagent (0.1 M sodium acetate, 0.01 M P-nitrophenyl phosphate, 0.1% Triton-X 100) were added to each well, the plates were incubated at 37 C for two hours, then 10 μL of 1 N NaOH were added to each well. Optical density of each well was read at 405 nm on a Biotek ELISA reader. Optical density has been shown to be directly related to cell number with this method. A linear correlation between optical density and cell number in our assay was confirmed by trypsinizing and counting the number of cells in parallel wells. Results are expressed as a percentage of the optical density in untreated control wells and represent the mean of at least three wells per point. Control values had a standard error of the mean of less than 10%.

Four classes of compounds were assayed for their ability to inhibit tumor-cell attachment in this system. The first group tested were potential or known modulators of extracellular matrix metabolism. These included heparin (Hepar Industries Inc., Franklin, OH), hydrocortisone-21-phosphate disodium salt (Sigma Chemical Co., St Louis, MO), 4-pregnene-17-alpha-21-Diol-3,20-Dione (cortexolone; Steraloids Inc., Wilton, NH), and combinations of heparin with hydrocortisone or cortexolone. An inhibitor of total protein synthesis, cycloheximide (Sigma), and a specific inhibitor of collagen deposition, the proline analogue L-azetidine-2-carboxylic acid (LACA; Calbiochem, La Jolla, CA), were also tested.

The second category of compounds tested were enzymes that are commonly used to disrupt cell adhesive contacts during passaging of cultured cells. We studied the general protease, trypsin, in a tissue culture formulation that included a calcium chelator (trypsin-EDTA; GIBCO). The bacterial neutral protease, Dispase (Collaborative Research, Bedford, MA) was also tested.

The third class of compounds included large molecular weight polymers, such as dextran (10,000 MW; Sigma), agarose (Sigma), and polyethylene oxide[4] (35,000 MW and 100,000 MW; provided by Cynthia Sung, Department of Chemical Engineering, MIT). These polymers were tested for their ability to physically interfere with cell attachment by altering medium viscosity.

The final group of test compounds included small synthetic peptides, such as glycine-arginine-glycine-asparate-serine-proline (GRGDSP; Peninsula Labs, Belmont, CA) and glycine-arginine-glycine-asparate-serine (GRGDS; Peptides International, Lexington, KY), which can specifically interfere with binding of fibronectin to cell surface receptors.[5] These peptides contain the RGD sequence that has previously been shown to be responsible for most of the cell binding activity of fibronectin. A related peptide that contains a single amino acid substitution, glycine-arginine-glycine-glutamate-serine-proline (GRGESP; Peninsula Labs), was also tested.

To determine whether inhibition of cell attachment was reversible, B16-F10 cells were incubated for 16 hours in the presence of LACA (100 μg/mL), Dispase (5 units/mL), GRGDSP (125 μg/mL), or GRGDS (125 μg/mL). Unattached cells were then collected, washed twice with serum-containing medium, and replated on gelatinized 96-well plates in new culture medium. Control cells were handled in a similar manner except that because they attached to the plates after 16 hours of incubation, they were collected by trypsinization. After incubation for four hours (LACA and Dispase) or 16 hours (GRGDSP and GRGDS), the medium was aspirated, wells were washed twice with 200 μL of PBS, and remaining attached cells were trypsinized and counted on a Coulter counter.

Inhibition of Tumor-Cell Implantation In Vivo

Two inhibitors of tumor-cell attachment *in vitro,* Dispase and GRGDS, were tested for their ability to block tumor-cell implantation in a surgical wound. Wounds were made on the backs of C57 B1/6 mice with scissors invisibly contaminated by B16-F10 melanoma, as described above. Wounds were then vigorously irrigated with 3 mL of Ringers lactate, either alone or supplemented with Dispase (5 units/mL) or GRGDS (1 mg/mL). Excess fluid was expressed and the wound closed with skin clips. On day 21, 30, and 45 after surgery, the number of animals that developed tumors was determined and the maximal length and width of each tumor was measured using calipers. Tumor volumes were calculated using the following formula:

$$\text{length} \times (\text{width})^2 \times 0.52 = \text{tumor volume (mm}^3)$$

Results

Contamination of Surgical Instruments by Tumor

In total 87% of the mice developed new tumors when scissors that had been previously contaminated with tumor cells from another animal were used to make the wound. However different tumor types varied in their ability to reimplant by this method (Table 1). Interestingly 100% of mice developed tumors when wounds were contaminated by instruments that were contaminated with B16 melanoma cells, whether the wounds were irrigated with saline, distilled water, or nothing at all.

TABLE 1. *Tumor-Cell Implantation in a Surgical Wound*

Tumor Type	n	Number of Tumor Cells on Scissors (±SD)	Animals with Tumors (%)
Lewis lung	23	4050 ± 495	87
B16 melanoma	28	2750 ± 2050	100
Reticulum-cell sarcoma	10	9700 ± 4667	90
MB-49 bladder	10	1013 ± 265	50

Inhibition of Tumor-Cell Attachment In Vitro

A variety of tested substances had little or no effect on tumor-cell attachment to gelatinized plates in the presence of serum-containing medium. Some substances, however, did inhibit this process. Combinations of heparin (100 μg/mL) and cortexolone (10 to 200 μg/mL) or hydrocortisone (12.5 to 200 μg/mL), which have previously been shown to modulate matrix metabolism in embryonic tissues *in vivo*,[6,7] produced less than 20% inhibition of tumor-cell attachment at either 4 or 16 hours of incubation (Fig. 1). Heparin (12.5 to 200 μg/mL), hydrocortisone (12.5 to 200 μg/mL), and cortexolone (10 to 200 μg/mL) had no effect when administered alone. High-dose cycloheximide (100 μg/mL) was only minimally effective after four hours of incubation, although lower doses completely inhibited attachment after 16 hours (half maximal inhibition at 0.5 μg/mL). LACA also inhibited tumor-cell attachment at 16 hours when administered at doses greater than 25 μg/mL (Fig. 1) and these inhibitory effects were found to be reversible. Cells that were prevented from attaching by exposure to LACA were able to replate in fresh medium when transferred to new dishes (reattachment was more than 50% of control attachment).

Trypsin, a general protease, had no inhibitory effect on attachment after 4 or 16 hours. In contrast Dispase completely prevented cell attachment after four hours (Fig. 2). The inhibitory effect of Dispase was maintained after 16 hours of incubation (half maximal inhibition 0.8 caseinolytic units/mL) and was reversible. Almost all of the cells that were prevented from attaching to the substrate replated in fresh medium (reattachment was 83% of control).

Agarose partially blocked attachment at 4 and 16 hours when used at high concentrations; an effect that coincided with increased viscosity of the solution (Fig. 3). In contrast neither polyethylene oxide (35,000 MW at 0.5 to 100 mg/mL or 100,000 MW at 0.25 to 50 mg/mL) nor Dextran (0.0025 to 25 mg/mL) produced a viscous solution or prevented cell attachment.

The synthetic peptide GRGDSP, which contains the RGD cell-specific binding sequence of fibronectin, inhibited tumor-cell attachment at concentrations greater than

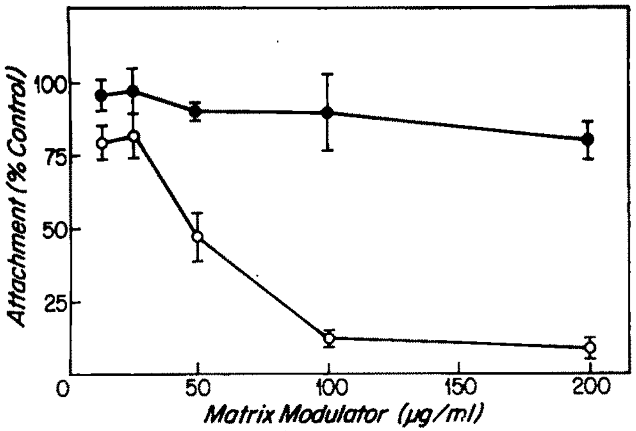

FIG. 1. Effects of modulators of extracellular matrix metabolism on tumor-cell attachment. L-azetidine 2-carboxylic acid (LACA) (O–O), a specific inhibitor of collagen deposition, completely inhibited B16-F10 melanoma-cell attachment to gelatin. Varying amounts of hydrocortisone (•—•), administered in combination with heparin (100 µg/mL), were only minimally effective (16-hour incubation; mean data is presented ± SEM).

10 ug/mL (Fig. 4). A concentration of 1 mg/mL completely inhibited attachment at four hours. The related peptide, GRGESP, also inhibited attachment but was significantly less effective than GRGDSP (Fig. 4). Cells prevented from attaching for 16 hours with GRGDSP could replate in fresh medium (reattachment was 80% of the control cells). Similar reversible inhibition of tumor-cell attachment was obtained with GRGDS (not shown).

Inhibition of Tumor-Cell Implantation In Vivo

Irrigation of a wound contaminated by B16-F10 melanoma cells with Ringers lactate containing either Dispase or RGD-containing peptide markedly delayed the appearance of tumor growing in the contaminated wound (Fig. 5). All of the animals in the group irrigated with Ringers lactate alone died within 6 weeks of the initial procedure. In contrast 25% of the group with GRGDS-irrigated wounds and 50% of the animals with wounds irrigated with Dispase were still alive at 6 weeks. Furthermore the average volume of tumors that formed was significantly smaller in the drug-treated animals than in controls (Fig. 5). Most importantly three mice (25% of animals) from the Dispase-treated group never developed tumors. All of the surgical wounds produced in these experiments healed without breakdown or infection; all deaths were due to tumor growth.

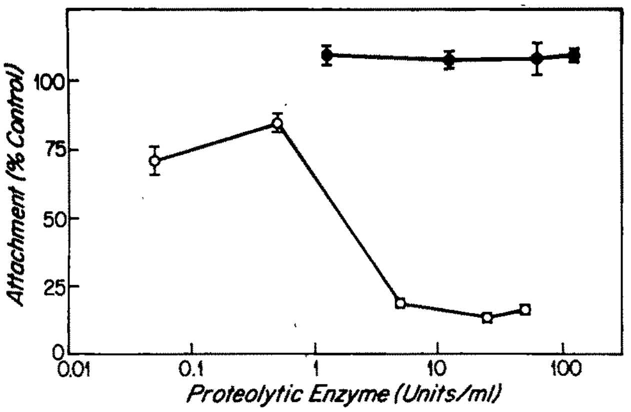

FIG. 2. Prevention of tumor-cell attachment using proteolytic enzymes. Dispase (O–O) (caseinolytic units) inhibited B16-F10 melanoma-cell attachment to gelatin-coated dishes, while Trypsin (•—•) (BAEE units) did not (4-hour incubation; mean data is presented ± SEM).

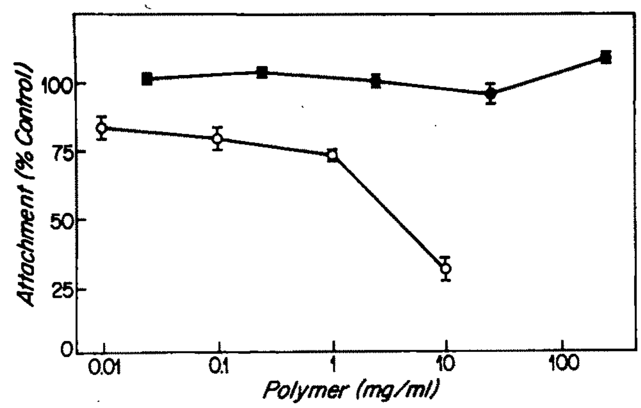

FIG. 3. Inhibition of tumor-cell attachment by altering medium viscosity. Agarose (O–O) partially blocked B16-F10 melanoma-cell attachment to the collagen matrix at concentrations that were highly viscous. Dextran (•—•) had no effect (4-hour incubation; mean data is presented ± SEM).

Discussion

These data suggest that implantation of free tumor cells in a surgical wound may be an underappreciated cause of local tumor recurrence. In surgical practice it is easy to imagine that scissor tips cut across microscopic exten-

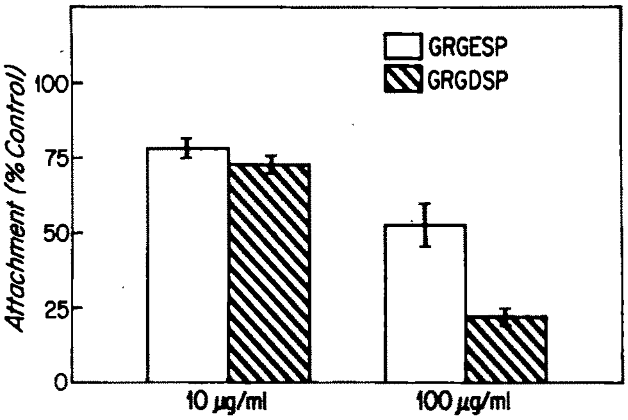

FIG. 4. Inhibition of B16-F10 melanoma-cell attachment using fibronectin-related peptides. On gelatinized dishes, both GRGDSP and GRGESP inhibited cell attachment, although the RGD-containing peptide was more effective (4-hour incubation; mean data is presented ± SEM).

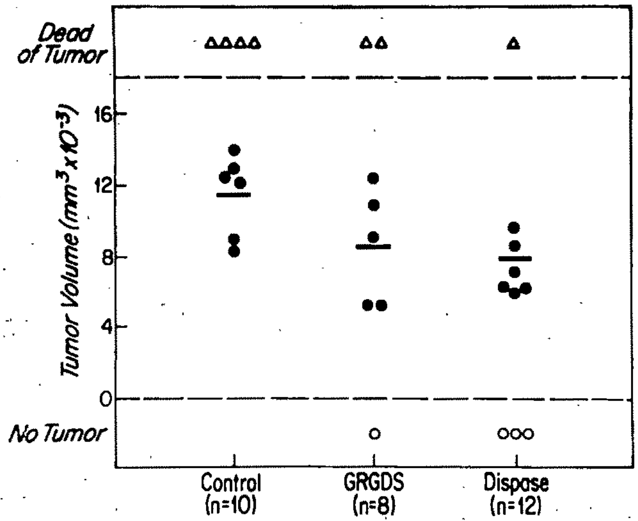

FIG. 5. Inhibition of B16-F10 melanoma implantation in a surgical wound with compounds that block tumor-cell attachment *in vitro*. Wounds were contaminated with B16-F10 melanoma cells as described in the text. Irrigation of the wound with GRGDS (1 mg/mL) or Dispase (2 units/mL) delayed the appearance of tumors compared to control (irrigation with Ringers lactate). Scatter plot shows animals that did not develop tumors (O), animals that died (△), and the volume of the tumors that were present in living animals (·) 30 days after contamination. Horizontal bar represents the mean tumor volume in living animals with tumors.

sions of tumor tissue during dissection around a mass that is being excised with close margins. In the present study contaminated scissors that were visibly clean consistently produced tumors at new sites. A major advantage of using an animal model system is that we could use scissors that had been contaminated by an exposed tumor in another animal. Therefore there was no possibility that subsquent tumors developed from a nidus of disease that had been missed during a resection, or from a systemic metastasis to the wound.[8]

The degree to which scissors became contaminated as a result of only two snips into tumor tissue was variable in our system and was related to the type of tumor (Table 1). Results also varied slightly with the method of cell counting; counts with a hemacytometer tended to be more accurate because multicellular clumps could be more easily distinguished. Nevertheless our results clearly demonstrate that an extremely low number of cells (a few thousand) could cause tumors in a high percentage of cases. This finding reflects the virulence of transplantable tumor models. Other investigators using a transplantable mast-cell tumor also have shown that a suture pulled through a slurry of cells reliably produces a tumor when it is then passed through the leg of another mouse.[9] In patients the presence of tumor cells in the wound does not necessarily mean that there will be a local recurrence.[10] This suggests that the implantation of these cells is a relatively inefficient process, similar to hematogenous metastasis.[11] However tumor cells probably implant more efficiently in a wound than they do on surfaces covered with intact epithelium or endothelium.[12] There are also clinical reports of tumors growing from cells innoculated by contaminated surgical instruments.[13] Thus our results justify traditional concerns about violating a tumor during surgery and suggest that instruments used during dissection around a tumor should not be used afterwards.

What else should be done? Adjuvant radiation therapy and systemic chemotherapy are often used, but toxicity makes it unwise to use these modalities without specific indications. Surgeons often fill the operative field with distilled water in an effort to lyse free tumor cells. Such treatment did not prevent tumors from developing in our experimental system. Past experiments have shown that flooding the wound with cytotoxic agents such as nitrogen mustard and formaldehyde can prevent tumor growth in the wound.[14] However this approach has not found much clinical favor because of concerns about wound healing and because it seems more sensible to administer cytotoxic adjuvant therapy systemically.

We propose that inhibition of cell attachment may be an effective way to prevent local recurrence due to implantation of tumor cells. Cell attachment to underlying extracellular matrix is an active process and the initial step that a free tumor cell must reach to grow into a vascularized tumor mass.[15] Unattached cells may well be more vulnerable to host immune responses and cells unable to attach would certainly be more easily displaced from a wound or serous cavity by irrigation. Finally cell geometry itself can exert a cytotoxic effect, especially with more highly differentiated tumor cells because these cells rapidly lose viability when maintained in a round, unattached state.[16,17]

To find agents that might accomplish this objective, we used a simple *in vitro* assay. Cell adhesion was promoted by the presence of adsorbed gelatin (*i.e.*, denatured collagen) as well as serum attachment factors (*e.g.*, fibronectin and vitronectin). Our assay is an initial approximation of the wound environment in as much as wounds contain serum as well as fibrillar and denatured (air dried, cauterized) collagens. However because it does not completely mimic the *in vivo* process, agents that inhibit cell attachment in this assay require *in vivo* testing to determine their real effectiveness. Nevertheless we expect that most compounds that cannot prevent tumor-cell attachment in this system will also be ineffective *in vivo*, and therefore consider the assay to be a useful initial screen.

Agents that modulate matrix metabolism take advantage of the dynamic nature of the attachment process because cell-matrix attachments are constantly being made and broken. Agents that tip the balance toward degradation should inhibit maintenance of cell attachment. A general inhibitor of protein synthesis, cycloheximide, only minimally inhibited initial attachment but did result in significant detachment at later times. Cycloheximide previously has been shown to inhibit migration and invasion;[18] however these effects may in part be due to associated cytotoxicity.

Proline analogues, such as LACA, have been previously shown to inhibit attachment of both normal and tumor cells by blocking collagen deposition.[19,20] Interestingly LACA prevented tumor-cell attachment after 16 hours in the present study, even though we used collagen- coated plates. A possible explanation for this finding is that B16-F10 melanoma cells require basement membrane collagens or native interstital collagens, which they would have to synthesize in our system to remain attached.

Combinations of heparin and steroid that were previously shown to inhibit collagen accumulation *in vivo* were minimally effective in preventing B16-F10 melanoma-cell attachment. Heparin and steroid combinations cause regression of growing capillaries *in vivo*, an effect mediated by dissolution of capillary basement membrane and subsequent detachment of associated endothelial cells.[6,7] The matrix- modulating effects of these combinations may be specific for endothelial cells or for vascular mesenchyme. Additional disadvantages of these types of matrix modulators are the time it takes to achieve an effect and the possibility that such agents would inhibit wound healing *in vivo*.

The second type of agent tested enzymatically disrupt cell-matrix attachments. Trypsin and Dispase are both proteolytic enzymes used in tissue culture to detach cells from culture substrata. The inability of trypsin to inhibit attachment in this assay was not surprising because there are high concentrations of trypsin inhibitors in normal serum. Dispase is a neutral protease made by *Bacillus polymyxa*, which is not toxic. It is used for a wide variety of applications, including lifting epithelial cells from culture dishes as a sheet rather than as a dispersed cell suspension.[21] These findings suggest that proteins that mediate cell attachment to extracellular matrix may be preferentially degraded by Dispase. Our results clearly demonstrate that Dispase can also inhibit tumor-cell attachment to gelatinized dishes, even in the presence of serum. More importantly we have shown that Dispase effectively inhibits tumor-cell implantation *in vivo*. The usefulness of Dispase *in vivo* could be limited by its ability to detach normal cells from their basement membrane. However it is important to emphasize that concentrations of 2 to 5 units/mL injected into a wound or intraperitoneally were well tolerated by C57 B1/6 mice.

Increased viscosity also appeared to prevent tumor-cell attachment in our *in vitro* assay. Agarose caused partial inhibition at concentrations that were still liquid, but most of its inhibitory effect appeared at higher viscosities that probably inhibit cell attachment as a result of physical entrapment. Such an effect could be worthwhile *in vivo* as a means to prevent tumor cells from being nourished or vascularized. However healing through a solid slab of agarose gel may be difficult and infection a problem.

Specific interference with binding sites important for cell attachment is an alternative approach. Peptides containing the RGD sequence from the cell adhesion site on fibronectin effectively inhibited tumor-cell attachment *in vitro* in a reversible fashion. Relatively high concentrations of RGD containing peptide were required in this assay most likely because of the presence of high concentrations of fibronectin in serum as well as the use of collagen rather than fibronectin as a substrate. The control peptide sequence GRGESP also inhibited B16-F10 melanoma cell attachment but less effectively than GRGDSP. These results are consistent with the finding that both of these synthetic peptides inhibit B16-F10 melanoma-cell spreading on fibronectin.[22] Importantly solutions containing RGD peptides also inhibited tumor-cell implantation *in vivo*, although not as successfully as Dispase. Due to its lack of toxicity, much higher concentrations of RGD peptides may be used in future studies. Others have shown that RGD peptides can decrease experimental hematogenous metastases, presumably by preventing blood-borne cells from attaching to pulmonary capillary extracellular matrix.[23]

Further understanding of the specific mechanisms and molecules involved in tumor-cell attachment to extracellular matrix presents new therapeutic opportunities. For example peptide fragments of laminin, alone[24] and in combination with heparin-binding fragments of fibronectin,[25] have been shown to inhibit experimental metastases. Such combinations may be more immediately used to prevent local tumor recurrences because this is the one clinical situation in which therapeutic intervention can coincide with the initial release of tumor cells. In our study two compounds, Dispase and GRGDS, which reversibly inhibited tumor-cell attachment *in vitro*, also decreased the chance that a tumor would develop in a wound contaminated by tumor cells on surgical instruments. When tumors did develop after wound irrigation with either compound, their appearance was delayed and their growth rate was suppressed. The use of combined modalities, including immunologic adjuvants such as muramyl dipeptide,[26] in conjunction with agents that block attachment is another as-yet-unexplored therapeutic possibility. Nevertheless it is important to emphasize that 25% of mice contaminated with tumor cells and treated with Dispase alone are alive, healthy, and tumor free to this date (more than 5 months after surgery).

Our data suggest that tumor cells seeded by surgical instruments can be a cause of local recurrence, and more importantly, one which is preventable at the time of surgery. Our first goal was to find a nontoxic compound that could prevent spilled tumor cells from implanting in a wound or serous cavity. A variety of compounds, categorized by their presumed mode of action, have been identified here. Although these specific agents may not ultimately prove valuable in clinical practice, we believe that this approach can be used to identify other effective agents. Thus we propose that inhibition of tumor-cell implantation may greatly benefit the subset of patients with localized neoplastic disease undergoing a local resection.

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Recent Trends in the Management of Desmoid Tumors

Summary of 19 Cases and Review of the Literature

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Recent advances in the understanding of desmoid tumor biology affect therapeutic choices. This series of 19 patients and review of the literature outlines historic perspectives and discusses the options in the management of these locally aggressive tumors. Desmoid tumors tend to grow steadily, regardless of tumor location. However differences in the aggressive nature of these tumors are seen when age and sex distributions are scrutinized. Although recurrence rates are high, excisional therapy is the best first approach. An exception is the case in which tumor excision is either particularly dangerous or likely to result in significant physical handicap. Radiation or drug therapy are most often used with recurrent disease or as an alternative to mutilating surgery. Although many pharmacologic approaches have been advocated, (including antiestrogen therapy, cyclic-AMP, and prostaglandin inhibition), results are anecdotal at best.

DESMOID TUMORS ARE infrequent. The descriptive name borrows from the Greek word "desmos," meaning band, or tendonlike. The world's collective literature to date records less than two thousand cases. However, because many surgeons see a scant number of these tumors during a routine career, the majority of isolated cases must certainly go unreported.

This collection of 19 patients and literature review that summarize recent developments in the understanding of desmoid tumor biology were stimulated by a patient with an abdominal wall desmoid tumor.

Materials and Methods

All hospital discharge and clinic records from January 1978 to January 1988 were reviewed on patients with the ICD.9 codes 238.1, 238.2, and 235.4 from the U.C.S.D. Medical Center and City of Hope National Medical Center (Duarte, CA). Pathology reports were verified to include only those patients with desmoid tumors (*i.e.*, aggressive fibromatosis). Desmoid tumors were categorized according to those found in the extremities or girdle muscles, in the abdominal wall, and in the mesentery. Cases were then tabulated with special reference to the episodes of desmoid tumors per patient (*i.e.*, recurrences), location of tumor, number of months until surgical procedure, type of surgical procedure, pathologic margins, adjunctive nonsurgical therapy, number of months until recurrence (if applicable), current disease status, and other medical conditions temporally related to the appearance or recurrence of these tumors.

Results

Table 1 summarizes our patient population. There were six male and 13 female patients. Twelve patients had extra-abdominal tumors, five had abdominal-wall tumors, and two had mesenteric desmoids. All but one of the male patients (with an abdominal-wall tumor) were in the extra-abdominal group. The mean age of the patients was 31.3 years (range, 5 to 59 years). The average age was 26.2 years for those with extra-abdominal desmoid tumors, 30.4 years for those with abdominal-wall tumors, and 36 and 59 years for the two patients with mesenteric tumors.

There were 42 surgical procedures performed on the 19 patients, six of which were limited to diagnostic incisional biopsies. The remaining procedures were attempts at surgical cures. All of the 19 patients are now alive. Six patients have recurrent disease, 12 are disease free at a follow-up of more than 6 months (probable cures), and one patient shows no evidence of recurrent disease at 1-month follow-up.

Five patients received radiation therapy in an effort to control recurrent extra-abdominal disease. None of these patients had control of their tumors after radiation therapy

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TABLE 1.

Patient No./Sex	Location	Months Until Excision	Type of Surgery	Margins	Additional RX	Months Until Recurrence	Current Status	Other Conditions
30F	Infrascapular	49	Excisional biopsy	Positive	Tamoxifen	2		
		2	Chest wall resection	Positive		50+	No evidence of disease	Childbirth (9/87)
30M	Finger	4	Excisional biopsy	Unclear		0		
		17	Ray amputation	Negative		3+	No evidence of disease	
24F	Upper arm	12	Excisional biopsy	Positive		6		Pregnancy
		7	Wide excision	Negative		6		
		6	Shoulder disartic	Negative		31+	No evidence of disease	
49M	Chest wall	1	Chest wall resection	Unclear	Potaba ×5 years	8		Gout, diabetes
		45	Extended excision	Positive	(Same)	1		
		115	Chest wall resection	Negative		42+	No evidence of disease	
20F	Sternum	3	Excisional biopsy	Unclear		12		
		0	Excision	Unclear		24		
		2	Excision	Positive	XRT ("maximum")	9		
		13	Excision with flap	Positive	Flap coverage	0		
		12	Clavicle excision	Positive		0		
		38	(re-excision planned)	—		—	Alive with disease (>96 mo.)	
20F	Calf	0	Biopsy	Positive	XRT (6600 cGy)	0		
		54	Excisional biopsy	Positive	Tamoxifen	56	Alive with disease (>7 mo.)	Pregnancy
13F	Foot	60	Excisional biopsy	Positive		35		
		1	Wide excision	Positive		1		
		10	Wide excision	Negative	Scar revision	82+	No evidence of disease	
5M	Neck/ mediastinum	3	Biopsy, tracheostomy	Positive		0		
		1	Partial resection	Positive	Chemotherapy	87	Alive with disease (>12 mo.)	Sepsis
37F	Subscapular	0	Biopsy	Positive		0		
		1	Neck disection	Positive	XRT (7480 cGy)	36		
		12	Chest wall resection	Negative		16+	No evidence of disease	
17M	Upper arm	36	Biopsy ×2	Positive		0		
		1	Excisional biopsy	Positive	XRT (5500 cGy)	0	Alive with disease (>6 mo.)	
14F	Hand	1	Excisional biopsy	Unclear		24		
		1	Excision	Unclear		36		
		1	Ray amputation	Positive	Scar revision	2	Alive with disease (>6 mo.)	
55M	Scalp	2	Excisional biopsy	Unclear		7		
		1	Excision	Positive	XRT (6000 cGy)	27+	No evidence of disease	
33F	Rectus abdominis	6	Excision, mesh repair	Negative		7+	No evidence of disease	Postpartum
23F	Abdomen-RLQ	17	Excisional biopsy	Positive		46+	No evidence of disease	
33F	Abdomen-RLQ	8	Excisional biopsy	Unclear		25+	No evidence of disease	
31F	Abdomen-RLQ	2	Excisional biopsy	Positive		6+	No evidence of disease	Appy scar site
32M	Abdomen	1	Wide excision	Positive	Chemotherapy	24+	No evidence of disease	Germ-cell CA
59F	Mesenteric	30	Biopsy	Positive		0		Rectal polyps
		19	Radical excision	Negative		44	No evidence of disease	
36F	Mesenteric	180	Biopsy	Positive	Clinoril, tamoxifen Colectomy, TAHBSO	0	Alive with disease (>75 mo.)	Gardner's Syndrome

Series of 19 patients. The data include the number of "tumor-burden" months before surgical procedure, the type of surgery performed, status of surgical margins, adjunctive therapy, the months until recurrence (or "disease-free" periods), current status of disease, and other medical conditions present.

alone. Of these five patients, three are alive with their disease and two are disease free 16 and 27 months after subsequent resectional therapy.

Two patients had chemotherapy, with no apparent effect on their tumor status. (A third patient with an abdominal-wall tumor had chemotherapy, but for an unrelated condition). Three patients had trials of the antiestrogen tamoxifen, with no apparent effect on their disease states. Only one patient had a trial of a nonsteroidal anti-inflammatory drug (Clinoril, Merck, Sharp, & Dohme, West Point, PA). She is now alive more than 6 years after total abdominal colectomy for polyposis coli (with Gardner's syndrome) and has confirmed residual mesenteric desmoid tumor.

Of the patients with no current evidence of disease, most have had a substantial period of tumor burden. In these 13 patients, who together had a cumulative disease time of 530 months, the average time from first symptoms until curative therapy was 40.8 months.

There were 20 episodes of tumor recurrence, all but one with positive surgical margins. (This represents the final pathologic reading, and not necessarily frozen section margins). Of the 12 patients without clinical evidence of tumor recurrence, five had positive tissue margins and seven had clear margins. These figures give an accuracy in predicting recurrence according to surgical margins of 81%, a sensitivity of 95%, and a specificity of only 58%. The positive predictive value of surgical margins was 79%, and the negative predictive value was 88%.

Discussion

John MacFarlane, in a 1832 compendium of cases from the Glasgow Royal Infirmary, described a mass that later came to be recognized as the first recorded case of a desmoid tumor.[1] Common usage of the descriptive term "desmoid" followed the naming of these tumors in 1838 by J. Muller.[2] The association of intra-abdominal desmoid tumors with familial *polyposis coli* was made in 1923 by Nichols,[3] and later reinforced in a series by McAdam and Goligher in 1970.[4] Radiation therapy for the control of desmoid tumors was first advocated by Ewing in 1928.[5]

Desmoid tumors comprise approximately 0.03% of all solid tumors, and 3.6% of the fibrous-tissue neoplasms. The annual incidence of these tumors is only 2 to 5 per million persons.[6] Reitamo has outlined four age distribution peaks in his series of 89 Finnish patients, with markedly different tumor characteristics found within each group.[6] In the juvenile peak (4.5 ± 3.5 years), girls outnumbered boys by 3:1, and extra-abdominal tumors predominate. In the fertile group (27 ± 4 years), abdominal-wall tumors were 11 times more frequent than the other types of desmoids, with the female:male ratio of 1.8:1. The middle-aged group (44 ± 7 years) also had predominantly abdominal-wall tumors (2.6 times higher incidence than other types), and no sex predominance. Finally in the old-age group (68 ± 4 years), no one tumor type or sex predominated.

The symptoms associated with desmoid tumors are few. Nearly all patients present to their physician with a mass. Pain is less frequent (~33%), and occurs primarily when tumors encroach joint or muscle mobility.[7,8] Bowel obstruction is seen with mesenteric desmoid tumors, but is separate and distinct from retroperitoneal fibrosis. That these tumors are found in association with Gardner's syndrome, a variant of familial polyposis coli, raises the issue of a genetic abnormality in collagen turnover regulation.[6] Alternatively a separate gene defect predisposing to desmoid tumors may be juxtaposed to the abnormality that transmits familial polyposis syndromes.

Desmoid tumors are located within the abdomen or trunk musculature in approximately 50% of cases, in the extremities in approximately 40% (usually referred to as extra-abdominal), and are mesenteric in less than 10% of patients.[6] They are commonly found in areas of previous traumatic or surgical scarring, and have been found in such obscure locations as the sphenoid bone[9] and surrounding CSF shunt tubing.[10]

Pathologically these tumors show a characteristic mass of interwoven spindle cells in bundles. There are varying amounts of collagen found within their matrix, with occasional sarcolemmic giant cells. Not infrequently the centers of the larger tumors are acellular. This whole constellation of findings resembles a low-grade fibrosarcoma. Importantly, however, only normal mitoses are found within the tumor. This partly accounts, at least in theory, for the poor response of these tumors to modes of therapy relying on cell-cycle kinetics.

The differential diagnosis of these tumors includes mainly other soft-tissue neoplasms (fibrosarcoma, liposarcoma, lipoma, and so on). However hernias, especially Spiegelian or incisional, as well as rectus sheath hematomas, can conceivably give a confusing picture. Intra-abdominal/mesenteric desmoids may be confused with lymphomas and retroperitoneal fibrosis.

Tumor Biology

Desmoid tumors are characterized by their propensity for slow, incessant growth and invasion of contiguous structures. Morbidity, while rarely associated with these tumors, occurs when there is encroachment on vital structures (*e.g.*, bowel obstruction by mesenteric desmoids, or invasion into the trachea or major blood vessels). Although locally aggressive, these tumors do not metastasize.

Many observers have noted that desmoid tumors show varying rates of growth. Whereas the growth rate of desmoids seems to be independent of the site of the tumor, the sex and the hormonal status of involved women affect the rate of growth.[6] Many have noted fast-growing tumors that are associated with pregnancy and tumor growth rates that seem to be lower in postmenopausal women. Desmoid tumors in male subjects average a growth rate of approximately 7.4 cm per year.[6] In the four age groups identified by Reitamo et al.[6] (mean ages, 4.5, 27, 44, and 68 years), the growth rates of tumors in women were 4.3, 19, 33, and 13 cm per year, respectively. The high rate of growth in hormonally active women underscores the suggestion that these tumors may be estrogen responsive.

Estrogen-receptor assays can be difficult to interpret because most tissues and tumors nonspecifically bind estrogen. However in a variety of studies 25% to 67% of desmoid tumors have been shown to bind estrogens in the same range seen in other estrogen-target organs ($K_d = 0.44 - 3.97$). Moreover, in one study, 79% of tumors bound antiestrogens (tamoxifen), whereas only 36% were estrogen-receptor positive.[11]

Control of Disease

Most authors believe that the best hope for the primary cure of this disease rests in total excision of the tumor. Unfortunately even when surgical margins are clear of tumor, recurrence rates are high. Table 2 compiles data from five recent studies that have reported substantial numbers of patients.[6,12–15] The overall recurrence rate with surgical excision alone was 40%. This recurrence rate is highest with mesenteric desmoids, presumably due to their necessarily limited surgical margins, but possibly also due to a genetic predisposition for this disease (see above).

It is of some interest that clean surgical margins do not necessarily guarantee a lower risk of recurrence.[6] This observation, along with similar data for the efficacy of adjuvant radiation therapy, probably speaks more for the selected (nonrandomized) nature of these reports than for the actual behavior of the tumors. It stands to reason that those patients with questionable or involved surgical margins will tend to populate the trials of adjuvant therapy. It is clear that no one parameter can predict the tendency of these neoplasms to recur. Re-excision of residual or recurrent disease is valid because recurrence rates following second and third excisions are equal to or lower than after the first attempt.[6]

TABLE 2. *Desmoid Tumor Recurrences (%)*
(Recent Studies with More Than 15 Patients)

		Tumor Location (%)			Treatment* (%)	
Reference	n	Abdominal	Extr'abd'l	Mesenteric	Surgery	Surg + XRT
Reitamo[6]	89	44 (9)	38 (45)	7 (NA)	74 (24)	6 (50)
Markhede[12]	44	—	44 (37)	—	41 (39)	3 (33)
Jones[13]	25	5 (40)	4 (50)	16 (81)	16 (81)	2 (100)
Khorsand[14]	19	5 (20)	11 (45)	3 (33)	12 (50)	6 (0)
Kiel[15]	222	45 (40)	172 (41)	5 (100)	222 (42)	8 (38)
Current series	19	5 (0)	12 (83)	2 (50)	13 (54)	5 (80)
Total	428	104 (24%)	281 (43%)	33 (77%)	378 (40%)	30 (43%)

* Not all patients received these treatment options, hence totals indicate fewer than all those with disease.

The number of patients at risk in each category is followed by the percent who had recurrent tumors (in parenthesis).

The literature on radiation therapy for desmoid tumors is largely addressed to extra-abdominal tumors. This is not only because of the difficult radiation fields with truncal and intra-abdominal desmoids, but also because radiation, as either adjunctive or primary therapy, is an attractive alternative to mutilating or debilitating extremity resections. Importantly because desmoid tumors grow slowly and do not metastasize, amputations and/or major muscle group excisions are considered too aggressive in certain cases. While most will have residual disease after radiation, many will have acceptable responses and potential control of their extra-abdominal disease.[15,16]

There have been a variety of pharmacologic approaches in the effort to control desmoid-tumor growth, especially for troublesome recurrences. These modes of therapy include c-AMP modulators (theophylline, chlorothiazide, ascorbic acid, testolactone), various chemotherapeutic agents, estrogen blockade, and prostaglandin manipulation.[17–20] There have been no convincing results from the conventional antineoplastic approach of either c-AMP or chemotherapy manipulations. This is probably due to the low mitotic index seen in these tumors. In uncontrolled studies, there have been reports of regression of tumors with estrogen blockade.[19] This is presumably a result of restricted RNA synthesis and altered gene transcription, but may also be an indirect effect through the inhibitory effect of estrogens on prostaglandin synthesis.[20]

The use of prostaglandin manipulation for desmoid tumors began with the observation that experimentally induced fibrosarcomas in rats regress with prostaglandin blockade.[21] Since then a variety of agents have been tried (again in poorly controlled studies with few cases), with hopeful response rates, including a recent case report regarding the use of Clinoril (sulindac).[20]

The most successful method of control, and best hope for cure of desmoid tumors, is complete excision. Re-excision of recurrent tumors is clearly warranted. Estrogen-receptor levels are of academic interest, but may justify hope for noninvasive therapy in the case of recurrent desmoid tumors. High-dose radiation therapy is also useful in the attempt to control recurrent disease, and may be appropriate as the primary therapy when the only alternative is a mutilating resection. Similarly trials of antiestrogens (even if receptor assays are low) and prostaglandin inhibitors may postpone, or possibly obviate, the need for aggressive surgical intervention when recurrent disease is encountered.

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Chest Injuries in Childhood

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Differences in anatomy and mechanisms of injury are believed to contribute to the unique response of children to thoracic trauma. To characterize the scope and consequences of childhood chest injury, we reviewed the records of 105 children (ages 1 month to 17 years, mean 7.6 years) with chest injuries admitted to a level I pediatric trauma center from 1981 to 1988. Nearly all injuries (97.1%) were due to blunt trauma, and more than 50% were traffic related. Rib fractures, commonly multiple, and pulmonary contusions occurred with nearly equal frequency (49.5% and 53.3%, respectively), followed by pneumothorax (37.1%) and hemothorax (13.3%). One fourth of all pneumothoraces were under tension. Significant intrathoracic injuries occurred without rib fractures in 52% of cases with blunt trauma. Associated head, abdominal, and orthopedic injuries were present in 68.6% of children reviewed. One in five received endotracheal intubation and ventilatory support for 1 to 109 days. Presence or absence of head injury neither increased the need for respiratory support (29.4% *vs.* 17.2%, respectively; $p = 0.24$) nor affected the duration of support for those who were ventilated (6.8 ± 8.9 days *vs.* 3.3 ± 2.6 days, excluding one ventilator-dependent head-injured patient and five early deaths). The presence of associated injuries, intubation, and pneumothorax or hemothorax all resulted in significantly longer hospitalizations and more severe injury as measured by Injury Severity Score (ISS). Age, rib fracture, and contusion had no effect. Rarely encountered were ruptured diaphragm (2 cases), transection of the aorta (1), major tracheobronchial tears (3), flail chest (1), and cardiac contusion (2). Only two of the three children with penetrating injuries and three of the 83 (3.6%) with blunt injuries underwent chest operations. Six children (7%) died, one from a penetrating injury and five from blunt mechanisms. Chest Abbreviated Injury Scale (AIS) and ISS correlated significantly with mortality; age and head AIS did not. Rib fractures, lung contusions, and associated head, abdominal, and skeletal injuries are common because of the predominance of blunt-injury mechanisms. Nearly one half of chest injuries occurred without rib fractures. The need for ventilatory support is uncommon; when required, its duration is generally brief. Aortic transection, flail chest, and penetrating injuries more frequently encountered in adults and are uncommon in children. Thoracotomy generally is not required. These observations arise from (1) the compliant thoracic structures of children; (2) the fact that children, as passengers or pedestrians in motor vehicle crashes, are not subjected to the same high-speed chest impact to which adult drivers are subject; and (3) the fact that children usually are not exposed to gunshot and stab wounds that are so common in adult urban violence.

THE EVALUATION AND treatment of thoracic trauma is a central feature of the early assessment and management of the injured child because chest injury may lead to tissue hypoxia.[1] Difficulties may arise when managing thoracic injuries in children. They rarely occur alone and are often a component of major multisystem injuries. Differences in anatomy and mechanisms of injury distinguish childhood injuries from those of adults. Several authors have noted that chest injuries are uncommon in pediatric trauma, which may contribute to physicians' unfamiliarity with their recognition and management.[2-4] To characterize the scope and consequences of childhood chest injury, we reviewed the experience in a level I pediatric trauma center.

Materials and Methods

We reviewed the hospital records of all children admitted to the Children's Hospital of Pittsburgh with discharge diagnoses of chest injury (International Classification of Diseases, 9th Revision, Clinical Modification, 860–862.9 and 875.0–875.1). Final radiologic reports verified all rib fractures, contusions, and pneumothoraces. Admission notes that included the presence of tension

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pneumothorax on physical examination, or a rush of air produced at the time of chest-tube placement that was noted on the procedure record, established the diagnosis of tension pneumothorax. A shift of the mediastinum or inversion of the diaphragm noted on the chest film also made the diagnosis of tension pneumothorax, if this diagnosis was not noted on the clinical notes. Nursing flow sheets provided the presence and volume of hemothorax. A volume greater than 20% of the child's estimated blood volume (80 mL/kg) was used to distinguish Abbreviated Injury Scale (AIS) 3 and 4 thoracic-cavity injuries. Aside from this modification, the 1985 AIS[5] provided AIS and ISS data. Shock was defined as systolic blood pressure more than 20 mm Hg lower than values published in the Advanced Trauma Life Support Course Manual.[1] Clinical data included age, sex, mechanism of injury, associated injuries, surgical therapy, respiratory therapy, length of hospital stay (LOS), complications, and mortality. The chi square statistic analyzed contingency data. Student's t test and analysis of variance with repeated measures compared differences among means of different sets of data. We regarded $p<0.05$ as significant.

Results

From January 1981 through June 1988 (7.5 years), 105 children (78 boys, 27 girls) aged 12 days to 17 years (mean 7.56 years, Table 1) were admitted to the Children's Hospital with significant chest injuries. Only three (2.9%) were the result of penetrating injuries. The remaining 102 injuries (97.1%) were due to blunt trauma. Table 1 summarizes the different mechanisms of injury by age group.

Table 2 summarizes the major intrathoracic injuries present in 83 patients with blunt thoracic trauma. Rib fractures and contusions occurred with nearly equal frequency, and were present in 52 (49.5%) and 56 (53.3%) cases, respectively. Pneumothorax occurred less frequently (39 cases, 37.1%). Hemothorax was least common (14 cases, 13.3%). These injuries occurred infrequently as solitary injuries. More often they occurred in groups of two or more lesions in a single patient (56 patients, 53.3%). Evidence of tension pneumothorax, either on chest film or at the time of chest-tube placement, was noted in nine patients with pneumothorax (23.1% of all children with pneumothorax). Of the 52 children with rib fractures, 36 (69.2%) had more than one rib broken. Nine children had fracture of the first or second rib (17.3%); none underwent aortography or later had evidence of an aortic transection: Significant intrathoracic injuries occurred without rib fractures in 53 of 102 patients with blunt trauma (52%).

TABLE 1. *Mechanisms of Chest Injury by Age Group*

Age (yrs)	n	Abuse	MVA	MVPA	Fall	Sled	Bike	MCA	Pen'g	Other
0–4	33	5	10	6	1	1	0	0	1	9
5–9	39	0	7	16	3	3	4	0	1	6
10–17	33	0	5	5	6	2	7	2	1	4
Total	105	5	22	27	10	6	11	2	3	19

Abuse, child abuse; MVA, motor vehicle crash; MVPA, motor vehicle–pedestrian crash; MCA, motorcycle crash; pen'g, penetrating trauma.

TABLE 2. *Rib Fractures, Pneumothorax, Hemothorax, and Pulmonary Contusions in Childhood*

	Ages (years)			
	0–4	5–9	10–17	Total
N	33	39	33	105
Deaths	4 (12.1)*	1 (2.6)	2 (6.6)	7 (6.7)
Rib fracture(s)	19 (57.6)	17 (43.6)	16 (48.5)	52 (49.5)
Isolated	8	3	5	16
Pneumothorax	12 (36.4)	13 (33.3)	14 (42.4)	39 (37.1)
Isolated	3	3	4	10
Tension	4	1	4	9
Hemothorax	3 (9.1)	6 (15.4)	5 (15.2)	14 (13.3)
Isolated	1	0	1	2
Contusion	11 (44)	31 (79.5)	14 (42.4)	56 (53.3)
Isolated	5	10	5	20
Combinations	17 (51.5)	23 (59.0)	16 (48.5)	56 (53.3)

Combinations refer to rib fractures, contusions, pneumothoraces, and hemothorax occurring in groups of two or more lesions in single patients.
* Percentages are shown in parentheses.

Twenty-two children (21%) received endotracheal intubation and ventilatory support for 1 to 109 days. Of the 237 children with head injury (AIS of 2 or more), 11 were intubated (29.7%), compared to 11 of 64 children who had chest injury uncomplicated by head trauma (17.2%; p = 0.24). Excluding one long-term head-injured patient (on a ventilator for 109 days before transfer) and four children who died on the day of admission, the mean duration of intubation was 4.9 ± 6.6 days for the 17 remaining chest-injury patients. There was no significant difference in the duration of support between children with and without complicating head injuries (Table 3).

Seven children from the study group died, one from a penetrating injury and five from blunt mechanisms, yielding a mortality rate of 6.7% (Table 4). A fall through a window resulted in the death of a 5-year-old girl when a shard of glass lacerated her right ventricle. A 14-year-old died of uncontrolled bleeding from a fractured liver that required resection after a pedestrian accident; other injuries included a deep laceration of the lung that caused a tension pneumohemothorax. A 13-year-old died during operation for a transection of the aorta after a motor vehicle crash. A 17-year-old passenger in a car crash had progressive deterioration from a major cardiac contusion and pneumohemothorax from a lung laceration. Left

TABLE 3. *Head Injuries in Association with Chest Injuries, and Requirements for Ventilatory Support (duration of intubation in days)*

	Head and Chest			Chest Without Head		
Age (yrs.)	n	No. Intubated	Duration	n	No. Intubated	Duration
0–4	14	5	1*, 2*, 5, 5, 109*	17	4	1, 1, 2, 9
5–9	12	4	2, 2, 5, 30	24	2	4, 4
10–17	11	2	1, 4	23	5	1*, 1*, 1, 2, 6
Total	37	11	6.8 ± 8.9	64	11	3.3 ± 2.6

Values give durations of intubation as mean ± standard deviation and do not include cases marked by *: One long-term head-injured patient and four fatalities.

lower lobectomy and open cardiac massage failed to resuscitate him. A one-month-old thrown from a motor vehicle suffered avulsion of the right upper lobe that led to bilateral pneumothorax, the right under tension. She died despite right upper lobectomy. A 2-year-old and a one-month-old with rib fractures died from massive brain injuries from physical abuse.

Head AIS and age did not influence the mortality rate ($p>0.05$), in part due to the low mortality rate of the group. However chest AIS 4 or 5 as a group had a significantly higher risk of death compared to AIS 1 to 3. As expected children with ISS greater than 25 also had a higher mortality rate (Table 4).

Other injuries frequently complicated care and are summarized in Table 5. The mean ISS for the group was 18.5, reflecting multisystem injury. Associated head, abdominal, or orthopedic injuries doubled the ISS and resulted in a three- to fourfold increase in hospital stay compared to children with isolated chest injuries. Systolic hypotension more than 20 mm Hg below normal for age[1] complicated care in 17 patients (16.2%).

TABLE 4. *Deaths from Childhood Chest Injury*

Factor	Deaths (%)	Survivors
Age (years)		
0–4	4 (12.1)	29
5–9	1 (2.6)	38
10–17	2 (6.1)	31
Head AIS		
0–1	3 (4.3)	66
2–5	4 (11.1)	32
Chest AIS		
1–2	2 (8.3)	22
3	1 (2.1)	46
4–5	4* (16.7)	20
ISS		
Less than 10	0 (0.0)	33
11–24	1 (2.3)	43
Greater than 25	6* (21.4)	22

* $p < 0.05$.

TABLE 5. *Associated Injuries, Injury Severity Score (ISS), and Length of Hospital Stay (LOS)*

Injury	N*	ISS	LOS (days)
Chest only	33	11.9 ± 8.6	3.9 ± 4.0
Assoc. Injuries*			
Head	37	24.1 ± 10.2	16.5 ± 21.0
Abdominal	23	22.0 ± 7.3	15.1 ± 14.6
Orthopedic	38	19.8 ± 9.8	12.9 ± 13.3
All	105	18.5 ± 10.9	10.5 ± 15.2

* Total injuries exceed the number of patients because of multisystem injuries.

Table 6 summarizes other factors that had an influence on both LOS and ISS. The requirement for intubation and the presence of pneumothorax and/or hemothorax all resulted in significantly longer hospital stays. All three factors also reflected more severe injuries as measured by ISS. Analysis of variance failed to demonstrate significant interactions among the three factors. Age, chest AIS, and the presence of pulmonary contusion or rib fracture had no influence on LOS or ISS.

Only three penetrating injuries to the chest were encountered during this time. A 4-year-old fell through a window and had a laceration into her mediastinum from which she survived. Another fall through a window resulted in death in a 5-year-old when a shard of glass lacerated her right ventricle. A gunshot wound to the upper chest resulted in a tracheal injury, pneumothorax, and a lower cervical cord transection in a 16-year-old.

During the study period nine children suffered intrathoracic injuries that did not fall into the categories sum-

TABLE 6. *Influence of Age, the Presence of Head Injury, Intubation Requirement, and the Presence of Pneumothorax and/or Hemothorax on the Length of Hospitalization (LOS) and the Injury Severity Score (ISS)*

Factor	LOS (days)	ISS
Age (years)		
0–4	17.2 ± 24.2	20.3 ± 10.7
5–9	7.5 ± 6.9	19.4 ± 11.4
10–17	10.2 ± 15.2	17.6 ± 11.7
Intubation		
Required	17.2 ± 10.1*	27.6 ± 9.7*
Not required	9.2 ± 15.7	16.8 ± 10.3
Pneumothorax		
Present	13.1 ± 13.1*	23.9 ± 8.3*
Absent	8.9 ± 16.2	15.2 ± 11.1
Hemothorax		
Present	22.4 ± 29.7*	22.6 ± 8.9*
Absent	8.8 ± 11.0	18.0 ± 11.0
Total	10.5 ± 15.2	18.5 ± 10.9

* $p < 0.05$ by analysis of variance. F-values for interactions among groups were not significant.

marized in Table 2. An 8-year-old and a 10-year-old survived ruptured diaphragms from pedestrian accidents. Both required repair of splenic lacerations. A motor vehicle crash caused a right phrenic nerve palsy in a 3-year-old who survived with pulmonary contusion and severe closed head injury. Two children suffered cardiac contusions. A 17-month-old survived a cardiac contusion, tension pneumothorax, and bilateral pulmonary contusions resulting from a pedestrian accident. A severe cardiac contusion contributed to the death of a 17-year-old in a motor vehicle crash discussed above.

We encountered three major tracheobronchial injuries. The repair of a tracheal laceration (from an all-terrain vehicle accident) through a right thoracotomy was successful in a 12-year-old. Bilateral pneumothoraces and subcutaneous emphysema led to a diagnosis of a major airway injury, verified by flexible bronchoscopy. A 6-year-old suffered a short longitudinal tear of the posterior membrane of the intrathoracic trachea. This healed spontaneously after four days of ventilatory support without operation. The third case was the one-month-old with a fatal avulsion of the right upper lobe mentioned above.

Four children underwent thoracic angiography during the period for presumed aortic disruption, one of which was positive. This child, a 13-year-old, died during operation for a transection of the aorta following a motor vehicle crash, the only such injury encountered during the period.

Only six children underwent operation for chest injuries, two with penetrating injuries and four with blunt injuries. Two children who had penetrating injuries from falls through windows underwent sternotomy, one of whom died. Four of 102 children (3.9%) with blunt injuries underwent thoracotomy (all described above): the 17-year-old car crash victim with cardiac contusion and lung laceration, the 12-year-old with a successful repair of a tracheal laceration, the one-month-old with avulsion of the right upper lobe, and the 13-year-old with the transsected aorta.

Discussion

Blunt mechanisms predominated in our series. Unlike other urban pediatric trauma centers,[4,6–8] penetrating injury at our center is uncommon. Although penetrating injuries primarily afflict teenage boys, our male to female ratio of 2.8 was no different from Meller's ratio of 2.6 and Sinclair's of 3.0,[4,8] a reflection that boys are at increased risk in general for all causes of injury. Mechanisms of chest injury paralleled age-related causes of injury in general, with abuse and motor vehicle injuries being most common in the 0-to-4-year- old age group, pedestrian injuries in the 5-to-9 year-old group, and bike injuries in the 10-to-17-year-old group.[9]

Because the ribs of younger children are less mineralized and more pliable,[10] chest trauma frequently causes the rib to bend but not break. Our series confirmed that significant intrathoracic injury frequently occurs without bony injury in children. However we found that a rib fracture was as likely to occur (51%, 52 of 102 patients), compared to the 25% to 68% rates in other reports,[4,11,12] a frequency that we considered surprisingly high. The state of ossification of the ribs may have a lesser effect on fracture than previously expected because the prevalence of rib fractures among admitted patients was the same in the youngest and oldest age groups. This may be an artifact of chest-film interpretation because a greenstick rib fracture may be missed on a film taken soon after injury. The presence of a fracture at the site is later confirmed when subsequent films reveal callus at that site.[13]

The soft chest wall of children may confer less protection to the underlying lung parenchyma and allow direct transfer of energy to the underlying lung.[10] This may explain why more than one half of our patients suffered pulmonary contusion, and more than one third suffered pneumothorax. This was also noted by Smyth,[3] who found that pulmonary contusion occurred in 61.7% of a series of 94 children with chest trauma (86 were blunt), and was the most common lung injury encountered. Fewer of his patients had a pneumo- or hemothorax as a result of their injuries (15.9%) than what we observed (37.1% and 13.3%, respectively). As with rib fractures, the prevalence of these two lesions did not vary with age. Hemothorax was less common, reflecting the near absence of penetrating injuries.

Mechanical ventilation was used in 21% of cases, but generally was of short duration (average, 4.9 days, excluding early deaths and one child with an extensive brain injury requiring long-term respiratory support). It appears that chest injury produces a mild compromise of respiratory function that is usually well tolerated by the child. This contrasts with recent reviews from general hospitals serving largely adult patients, where more patients required ventilation for longer periods. Johnson found that 34 of 86 patients (39.5%) with pulmonary contusion required mechanical ventilation for a mean of 9.1 days.[14] In another study Clark found that isolated pulmonary contusion resulted in mechanical ventilation in 31%, but this increased to 57% to 59% if flail chest was also present. The mean duration of ventilation among survivors was 10.4 days.[15] Flail chest, an important prognostic determinant among their patients, was not a factor in our series because only one of our patients had flail chest. Thus the differences in the frequency of ventilator requirements and mortality rate may be due to differences in the prevalence of flail chest, which in turn may reflect differences in the magnitude of trauma among the largely adult reviews and our study.

Central nervous system injuries and hemorrhage, rather than respiratory insufficiency, caused most deaths in both Johnson's and Clark's studies,[14,15] an observation also noted in children by Sinclair.[8] This supports the view that the main determinant of prognosis in chest trauma is the presence of associated injuries, not chest injury alone. In Smyth's series the number of deaths from chest injury was higher when other major organ-system injuries were present.[3] We found that ISS provided a good estimation of the effect of associated injuries on mortality rate and was better than the number of associated organ systems injured (Table 4). We found that the severity of chest injury as estimated by AIS had a positive effect on mortality rate (Table 4), in contrast to the findings cited above.[8,14,15]

Pneumothorax and hemothorax significantly increased hospital stay (Table 5), whereas pulmonary contusion and rib fracture did not. Care and maintenance of a chest tube accounts, in part, for the difference in length of hospital stay, but pneumothorax and hemothorax were associated with patients who had significantly higher ISS (Table 6), and more associated injuries. This may indicate that these two injuries are associated with a greater transfer of energy, greater injury severity and, therefore, greater morbidity.

We failed to verify Smyth's observation that deaths from chest trauma were most frequent in the preschool age group (23%), decreasing to 11.3% in the 5-to-10-year-old and 8.3 in the 10-to-15-year-old groups.[3] Our mortality rate in the 0-to-4-year-old age group was the highest among the three divisions studied (12.1%), but the difference failed to reach statistical significance. Age also had no effect on the length of hospital stay. The difference in mortality rate between our results and those reported by Smyth may be due to the effect of differences in prehospital care and transfer.

TABLE 7. *Blunt Thoracic Trauma in 515 Adults[16] and 102 Children (present study)*

Factor	Adult	Children
Demographics		
Age in years (mean)	14–86 (36.9)	1 week–17 (7.5)
Male:female ratio	2.7	2.8
Mechanism of injury (%)		
Automobile accident	70.9	21.6
Pedestrian accident	9.5	26.4
Fall	7.6	9.8
Shock (%)	27.5	16.2
Death (%)	15.5	4.9
Injuries (%)		
Isolated chest injury	16.3	29.4
>2 extrathoracic systems	47.5	22.5
Rib fractures	71.4	51.0
Intrathoracic injury, no bony injury	24.7	49.0
Pneumothorax	18.4	37.1
% of pneumothoraces under tension	8.4	23.0
Hemothorax	37.4	13.3
Pulmonary contusion	26.0	53.3
Ruptured diaphragm	4.5	1.9
Aortic rupture	3.7	1.0
Tracheobronchial	0.8	2.9
Flail chest	12.2	0.9

TABLE 8. *Immediately and Potentially Life-Threatening Chest Injuries in Children*

Injury	No./7.5 Years
Immediately Life Threatening	
Airway obstruction	15*
Tension pneumothorax	9
Open pneumothorax	0
Massive hemothorax	14
Flail chest	1
Cardiac tamponade	2
Total	41
Potentially Life Threatening	
Pulmonary contusion	56
Myocardial contusion	3
Aortic transection	1
Diaphragmatic hernia	2
Esophageal disruption	0
Total	62

* During 1987, 2 of 605 patients admitted to our trauma service had airway obstruction.

Shorr and coworkers recently reported a large experience of blunt thoracic trauma from an adult trauma center.[16] A comparison of their results with ours illustrates the contrasts between adult and pediatric blunt chest injury (Table 7). The sex ratios are the same, reflecting that male patients of all ages are at increased risk of injury. Motor vehicle injuries predominated in both series, but incidences reflected age-related differences in exposure: adults spend more time in automobiles as drivers, while children spend more time on sidewalks as pedestrians.[17] Children were less frequently injured as passengers in motor vehicle crashes, in contrast to adults, in whom automobile crashes caused 70.9% of blunt chest injuries.

Differences in injury mechanisms probably account for some of the clinical differences between adults and children; shock, death, extrathoracic injury, and hemothorax appeared more frequently in Shorr's report than in ours. Developmental changes in anatomy may explain other differences: rib fractures and flail chest (more in adults), intrathoracic injury without fracture, and pulmonary contusion (more in children). Unexpected was the relatively high incidence of pneumothorax and tension pneumothorax among children. Tracheobronchial rupture and lacerations, rare injuries in blunt trauma, were also seen relatively more frequently in children (2.9% in our series; 5.8% of injuries reported by Smyth),[3] whereas rupture of the diaphragm and aorta are more frequent in the adult series. These differences may result from anatomic differences in the structural resistences to injury between adults and children.

Trunkey and Lewis[18] classified chest injuries into those that are immediately life threatening and those that are relatively life threatening. Table 8 summarizes the number of cases in our review that fell into these categories. A level I pediatric trauma center like ours will therefore encounter about 14 cases of life-threatening chest injuries per year, or a little more than one per month. The frequency of life-threatening injury is relatively low, but the potential for morbidity and death is high. Therefore one must maintain a high index of suspicion for significant chest injury during the pediatric trauma evaluation.

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Surgical Significance of Popliteal Arterial Variants

A Unified Angiographic Classification

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Distal popliteal arterial variations may influence the success of femorodistal popliteal and tibial arterial reconstructions. Two patients whose bypass procedures were initially unsatisfactory because of a poor choice for anastomosis stimulated a review of variations in the distal popliteal artery in 1000 femoral arteriograms. The popliteal arterial anatomy could be assessed in 605 extremities and the tibial arterial anatomy in 495 extremities. Seventy-five variant cases were identified. Normal branching of the popliteal artery was present in 92.2%. Among the 7.8% incidence of variants, the majority (72%) were either high origin of the anterior tibial artery or a trifurcation pattern. Of variant patterns to the foot (5.6%), the most common was that in which the supply to the distal posterior tibial artery arose from the peroneal artery. We propose a unified classification of the popliteal and tibial arterial variations that encompasses both anatomic areas. Variant arterial supply to the foot can be suspected when the infrapopliteal vessels show a hypoplastic or aplastic anterior or posterior tibial artery and compensatory hypertrophy of the peroneal artery. Knowledge of these variants is important to angiographers and vascular surgeons.

VARIATIONS IN THE anatomy of the distal popliteal artery have an influence on the success of femorodistal popliteal and tibial arterial reconstructions. Two patients whose initial arterial anastomoses were unsatisfactory because of a poor choice for the distal anatomic site of reconstruction stimulated a review of the variations in the distal popliteal and tibial arteries in the femoral arteriograms of 1000 extremities.

In this study we classify and relate variant patterns of the popliteal artery and the tibial arterial distribution to the lower leg. Seventy-five variant cases were classified, including one type that, to our knowledge, has not been reported previously in the radiologic or anatomic literature.

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We propose a modification of the classification of popliteal arterial variation suggested by Lippert,[1] in which attention to the predictability of variations in arterial supply to the foot is based on the appearance of the proximal tibial arterial anatomy.

Materials and Methods

Femoral arteriograms performed on 1000 extremities in the period from July 1, 1980 to December 31, 1986 were reviewed. The angiograms of 395 patients were excluded from analysis because of insufficient radiologic detail in the area of interest. The branching pattern of the popliteal artery was analyzed in 605 extremities. The arterial supply to the foot was analyzed in 495 extremities. The following measurements (based on Lippert's classification[1]) were made (Fig. 1). Distance A represents the vertical distance in centimeters between the medial tibial plateau and the origin of the anterior tibial artery (AT) in 286 extremities. Distance B represents the vertical distance between the origin of the AT and that of the peroneal artery (PR) in 220 extremities. Distance B represents the length of the tibioperoneal arterial trunk.

Results

The following classification includes variations in both the branching of the popliteal artery and the arterial supply to the foot. The relative incidences of variants were calculated (Figs 1 to 3).

I. Normal Level of Popliteal Arterial Branching (Fig. 1)

(A) Usual pattern: AT is the first arterial branch; tibioperoneal artery follows and bifurcates into the peroneal and posterior tibial (PT) arteries (560/605 = 92.2%).

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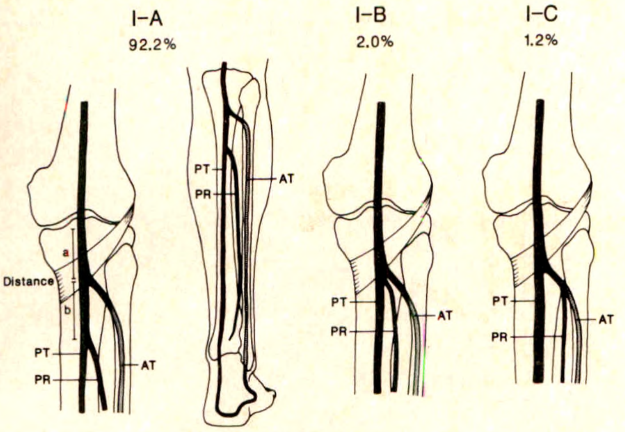

FIG. 1. Type IA: the usual pattern of popliteal arterial branching and arterial supply to the foot. Type IB: trifurcation: the anterior, peroneal, and posterior tibial arteries arise at the same point without an intervening tibioperoneal trunk. Type IC: the posterior tibial artery is the first branch. The anterior tibial and peroneal arteries arise from a common trunk.

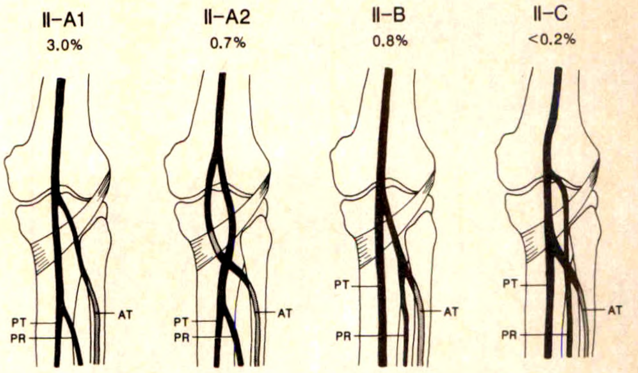

FIG. 2. Type IIA-1: the anterior tibial artery arises above the knee joint and has a straight course in its proximal segment. Type IIA-2: the anterior tibial artery arises above the knee joint but takes a medial swing, presumably resulting from its passage anterior to the popliteus muscle. Type IIB: the posterior tibial artery arises at the level of the knee joint. Type IIC: the peroneal artery arises above the knee joint.

(B) Trifurcation: AT, PR and PT arise within 0.5 cm; there is no true tibioperoneal trunk. 12/605 = 2.0%.

(C) Anterior tibioperoneal trunk: PT is the first branch, tibioperoneal trunk follows and bifurcates into the PR and AT. 7/605 = 1.2%.

II. High Division of Popliteal Artery (Fig. 2)

(A) AT arises at or above the knee joint (22/605 = 3.7%).

(1) Normal course of proximal AT (18/605 = 3.0%).

(2) Medial initial curve in AT (4/605 = 0.7%).

(B) PT arises at or above the knee joint. Common trunk for PR and AT (5/605 = 0.8%).

(C) PR arises at or above the knee joint. Common trunk for AT and PT (1/605 = 0.16%).

III. Hypoplastic or Aplastic Branching with Altered Distal Supply (Fig. 3)

(A) Hypoplastic-aplastic PT. Distal PT replaced to PR (19/495 = 3.8%).

(B) Hypoplastic-aplastic PT and AT. Dorsalis pedis (DP) replaced to PR (8/495 = 1.6%).

(C) Hypoplastic-aplastic PT and AT. PT and DP replaced to PR (1/495 = 0.2%).

The mean value for distance A was 6 cm with a range between 2.5 cm above the knee joint and 10 cm below. The mean value for distance B was 3.9 cm with a range between 0.4 cm and 13.5 cm.

Discussion

This review of popliteal and tibioperoneal arterial variations was stimulated by technical difficulties encountered during the performance of arterial reconstruction in two patients who required femorodistal bypass graft procedures.

In the first patient, the distal arterial anastomosis of an *in situ* saphenous vein bypass graft was made to a hypoplastic posterior tibial artery because it was not recognized by the surgeon that the posterior tibial distal arterial supply was from a proximal replaced peroneal artery (Fig. 4).

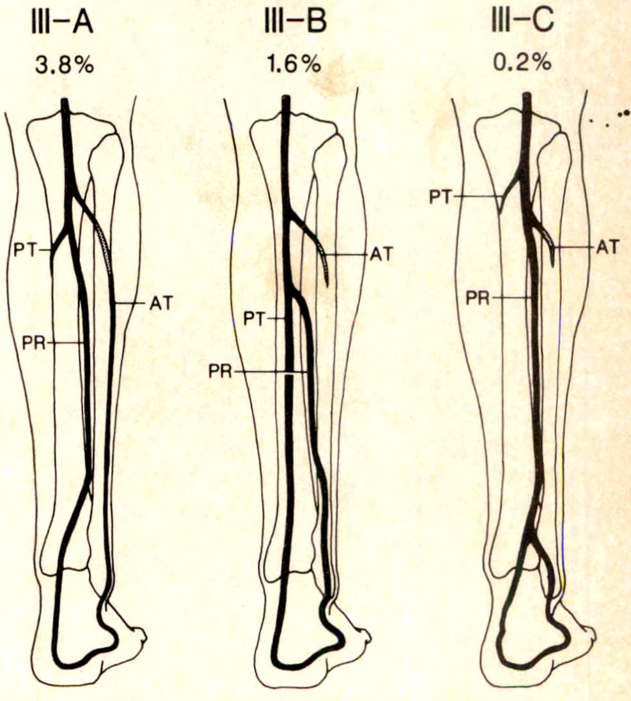

FIG. 3. Type IIIA: the posterior tibial artery is hypoplastic and the peroneal artery is large. At the ankle, the distal posterior tibial artery is replaced to the peroneal artery. Type IIIB: the anterior tibial artery is hypoplastic and the peroneal artery is large. At the ankle, the dorsalis pedis artery is replaced to the peroneal artery. Type IIIC: both the anterior tibial artery and the posterior tibial artery are hypoplastic. At the ankle the dorsalis pedis and posterior tibial arteries are replaced to the peroneal artery.

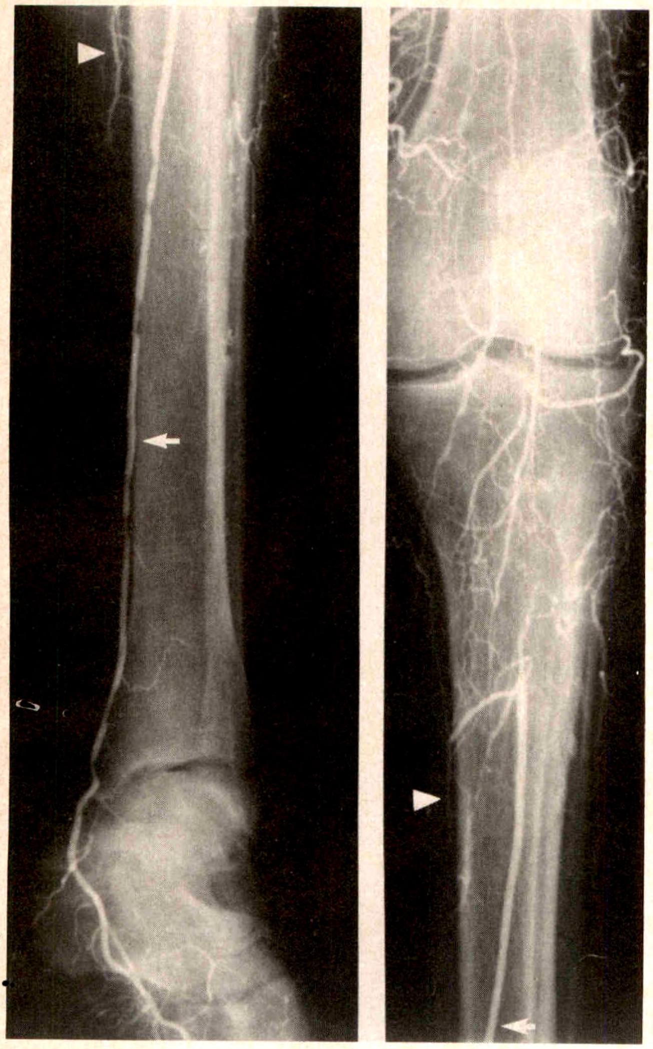

FIG. 4. Diagnostic arteriogram reveals a hypoplastic posterior tibial artery (arrowhead) and a hypertrophied peroneal artery (arrow). At the level of the ankle, the posterior tibial artery is replaced to the peroneal artery (Type IIIA).

The initial operative arteriogram (Fig. 5) shows extravasation because there was no outflow from this anastomotic site. Faint visualization of the peroneal artery can be seen on this film. When this error was recognized, the anastomosis was resited to the more medially placed peroneal artery, resulting in a strong pulse in the posterior tibial artery at the ankle. A second operative arteriogram shows this anastomosis (Fig. 5).

In the second patient (type II-B), the initial distal anastomosis was made erroneously to a common trunk of the AT-PR whose proximal end was stenotic and whose distal outflow was occluded at mid calf (Fig. 6). The posterior tibial artery, which supplied solitary run-off to the foot, was thereby excluded from revascularization (Fig. 7). Five days later revision to the posterior tibial artery was required because of thrombosis of the graft.

Tables 1 and 2 summarize the frequency of each subtype of arterial variation in our study and list those reported by previous authors using angiography[2-4] or limb dissection.[5-9] Our classification is a modification of Lippert's system.[1] The two major variants in the popliteal branching pattern are trifurcation (I-B) and high division with normal branching sequence (II-A). Our proposed classification includes an additional type of high division (IC). We have excluded variants not involving one of the three run-off vessels (AT, PR, PT), such as the island branch of the popliteal artery described by Adachi[6] and included in Lippert's system. We have followed Lippert's system of dividing the variants into those with normal level of division (I) and those involving a high division (II). Variants grouped into category III possess a normal branching pattern and sequence but involve a critical variation in arterial supply to the foot that can be predicted by observing the popliteal region even if visualization of the distal run-off is suboptimal. For this reason we in-

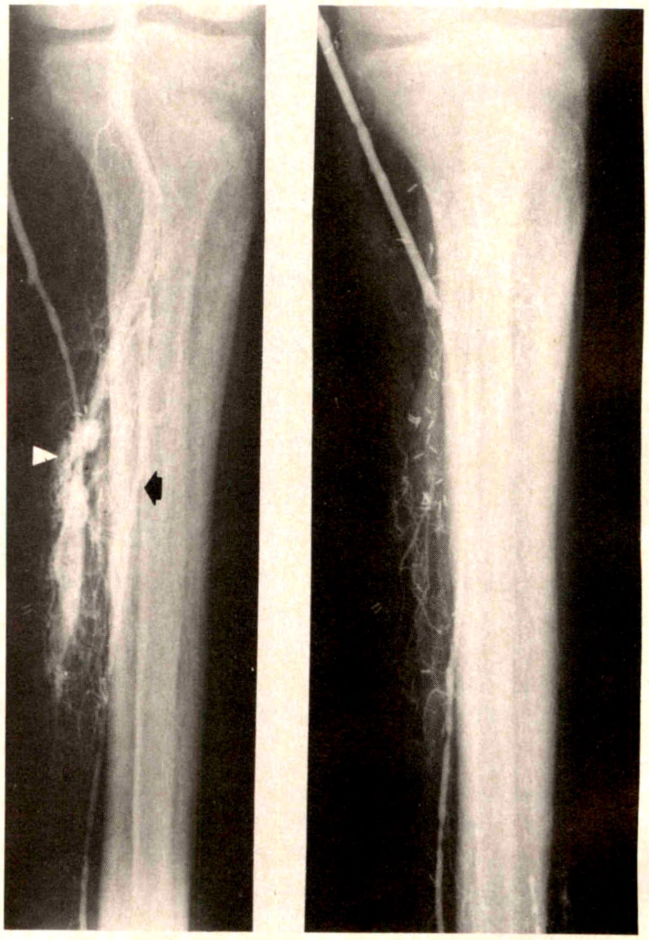

FIG. 5. Initial operative arteriogram (left) obtained following distal anastomosis to the hypoplastic posterior tibial artery (arrowhead). The peroneal artery is opacified (arrow). There is extravasation of contrast about the anastomosis. Second operative arteriogram (right) shows revision to hypertrophied replaced peroneal artery.

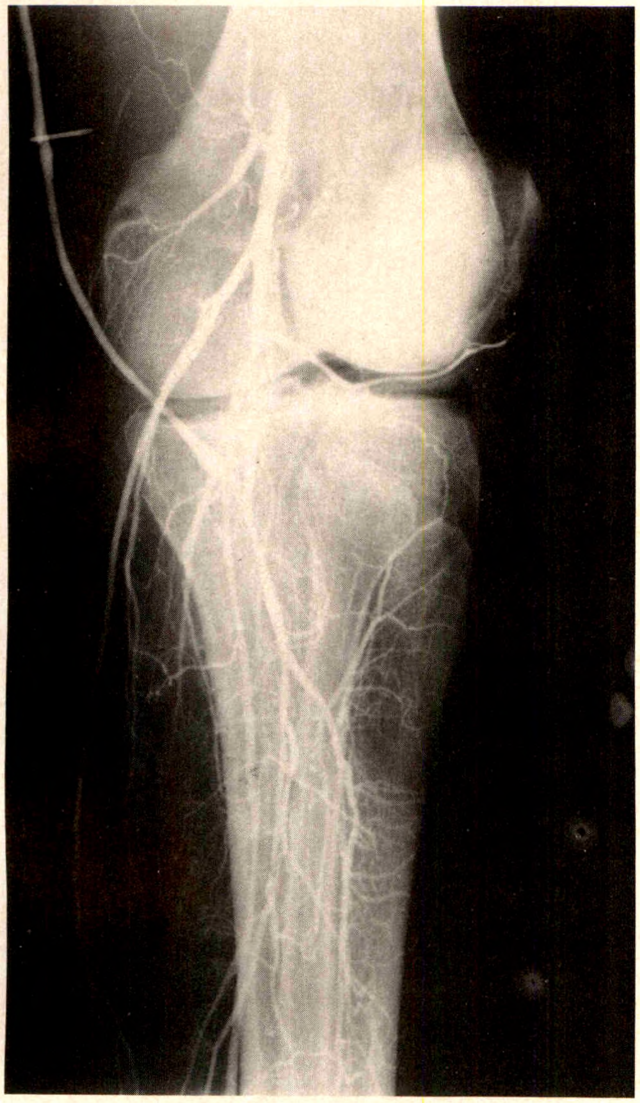

FIG. 6. Operative arteriogram obtained after the distal anastomosis to a common trunk of the anterior tibial and peroneal arteries distal to the origin of the posterior tibial artery.

cluded category III to provide a unified system that we believe will be of greater clinical relevance to vascular surgeons. These three categories are described more fully below.

Category I

Type I-A: usual pattern. The popliteal artery posteriorly divides to the inferior border of the popliteus muscle by giving off the anterior tibial artery, which courses laterally toward the fibula before running down the calf to terminate as the dorsalis pedis artery. In our study the mean distance between the medial tibial plateau and the origin of the AT is 6 cm. The subsequent segment of the main artery is known as the tibioperoneal trunk, which averaged 3.9 cm in our study. Morris determined mean values of 5.9 and 3.7 cm in his review of 246 extremity angiograms.[3] Bardsley found no correlation between the length of the tibia and the level of branching of the popliteal artery.[4] The tibioperoneal artery terminates at the point where the peroneal artery originates. The latter courses down the interosseous membrane to end slightly above the ankle in a mustache configuration, composed of the communicating branch to the PT and the perforating branch to the AT. The posterior tibial artery runs down the posterior calf and terminates at the level of the calcaneus by bifurcating into the medial and lateral tarsal arteries. The DP and PT supply the foot arcades, and there are multiple communications at these levels, as well as multiple variations.[9]

The reader is referred to the detailed work of Senior[10] for review of the embryologic development of the usual and variant patterns. Briefly, the lower extremity vessels arise from two sources: the primary limb bud artery (axial or sciatic artery, a branch of the umbilical artery), and the femoral artery. By the 14-mm embryonic stage, the femoral artery has grown into the thigh and joined the sciatic artery at the level of the adductor canal. Development of the run-off vessels is complete by the end of the third month. The popliteal and PR arise from the sciatic artery, whereas the AT and PT derive from the femoral system.

Type I-B: trifurcation. The AT, PR, and PT arise in close proximity posterior to the inferior border of the popliteus muscle. We have followed the criteria of Adachi wherein a trifurcation is described only if the common

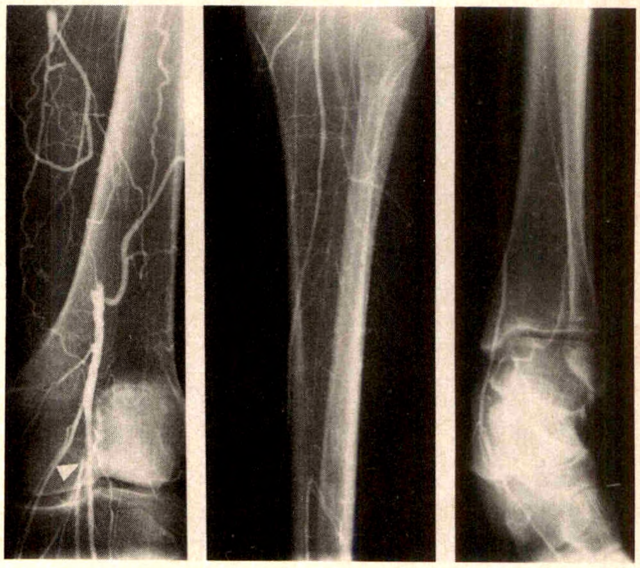

FIG. 7. Diagnostic arteriogram reveals the posterior tibial artery (arrowhead) arising from the popliteal artery at the knee joint (Type IIB). There is a significant stenosis of the popliteal artery at the origin of the posterior tibial artery. The anterior tibial and peroneal arteries are occluded proximally.

TABLE 1. *Frequency of Type I and Type II Popliteal Arterial Variations (Figs. 1 and 2)*

Author	Source	Extremities Examined	IA (%)	IB (%)	IC (%)	IIA-1 (%)	IIA-2 (%)	IIB (%)	IIC (%)
Kim, Orron	Angiography	605	92.6	2	1.2	3	0.7	0.8	<0.2
Mauro, 1988	Angiography	343	88	4.1	1.2	2.3		0.9	—
Morris, 1961	Angiography	246	88.6	2.9	1.2	3.6	—	0.8	—
Bardsley, 1970	Angiography	235	92.8	0.4	—	4.2	—	1.7	—
Quain, 1844	Dissection	258	90.3	2.3	6.6	0.8	—	—	—
Adachi, 1928	Dissection	770	96	0.8	0.5	0.9	1	0.8	—
Trotter, 1940	Dissection	1168	93.4	0.5	1.3	1.5	2.4	1.4	—
Keen, 1961	Dissection	280	90.7	4.3	0.4	3.6	0.4	1.1	—
Lippert, 1985	Dissection	—	90	4	1	3	1	1	—

—, no information available.

trunk following the origin of the first branch is less than or equal to 0.5 cm in length.[6] Morris found an incidence of 2.9% using these criteria.[3] However they also found an incidence of 2.9% of common trunks measuring more than 0.5 cm but less than 1 cm. Although the criteria of Adachi are anatomically more precise, it may well be that Morris' notion presents greater practical clinical use to the surgeon pondering potential sites for distal anastomosis.

Type I-C: anterior tibial-peroneal trunk. The PT is the first branch. The anterior tibioperoneal trunk bifurcates into the PR and PT. An incident reflecting the clinical significance of this variation was described above.

Category II: High Division of the Popliteal Artery

Anatomists consider division to be high if it occurs proximal to the inferior border of the popliteus muscle (PM). Because this level can not be determined angiographically, we used the superior edge of the medial tibial plateau as our cut-off point. In Table 1 we have excluded the cases reported in the anatomic studies in which division occurred between the superior and inferior borders of the PM. We have, therefore, assumed an equivalence of the superior border of the PM and the superior border of the medial tibial plateau because the anatomists did not consider the latter in their determinations.

Type II-A: AT arises at or above the knee joint. This is consistently the most frequent type of high division. Anatomists have described two subtypes. In the first (II-A1), the AT courses posteriorly to the PM; in the second (II-A2), the AT courses anteriorly to the PM. A review of sketches by Adachi reveals that in II-A2 the initial course of the AT takes a medial swing before crossing anteriorly to the PM.[6] We postulate this medial swing to be the result of the anterior course, and we found four such cases in our series.

TABLE 2. *Frequency of Type III Popliteal Arterial Variations (Fig. 3)*

Author	Source	Extremities Examined	IIIA (%)	IIIB (%)	IIIC (%)
Kim, Orron	Angiography	495	3.8	1.6	0.2
Mauro, 1988	Angiography	343		2.3	
Bardsley, 1970	Angiography	235	0.9	—	—
Adachi, 1928	Dissection	1239	—	7.1	—
Huber, 1940	Dissection	200	—	3	—
Keen, 1961	Dissection	280	2.5	5	—
Lippert, 1985	Dissection	—	5	6	—

—, no information available.

Type II-B: PT arises at or above the knee joint. This is the correlative of Type I-C, differing in that the PT arises high. As in Type I-C, an anterior tibioperoneal trunk is formed.

Type II-C: PR arises at or above the knee joint. This pattern was observed in a single case. The PR arose above the knee. A short (1.3 cm) anterior-posterior tibial trunk ensued. To our knowledge this variant has not been previously reported (Fig. 8).

Category III

The peroneal artery normally terminates into small branches that communicate with the AT and PT at the level of the ankle joint. In instances in which the proximal segments of the AT or PT are congenitally absent or hypoplastic, the respective branch of the PR will directly supply the distal distribution of the AT (the DP) or PT, which can, therefore, be considered replaced to the PR. In all our cases in this category, the pattern at the foot could be predicted by observing the area of the popliteal bifurcation because the hypoplastic or absent vessel was evident along with a concomitant increased caliber of the proximal PR. In the presence of this finding it is essential that the distal run-off is adequately demonstrated with particular attention paid to the nature of supply to the DP and PT at the ankle. Caution must be used to differentiate this phenomenon from atherosclerotic occlusive disease of the AT or PT, with the hypertrophied PR collateralizing the distal AT or PT. The presence of gradual tapering of the hypoplastic artery, the lack of collateral reconstitution distally, and a straight, nonundulating appearance of the distal segment of the PR reaching the DP

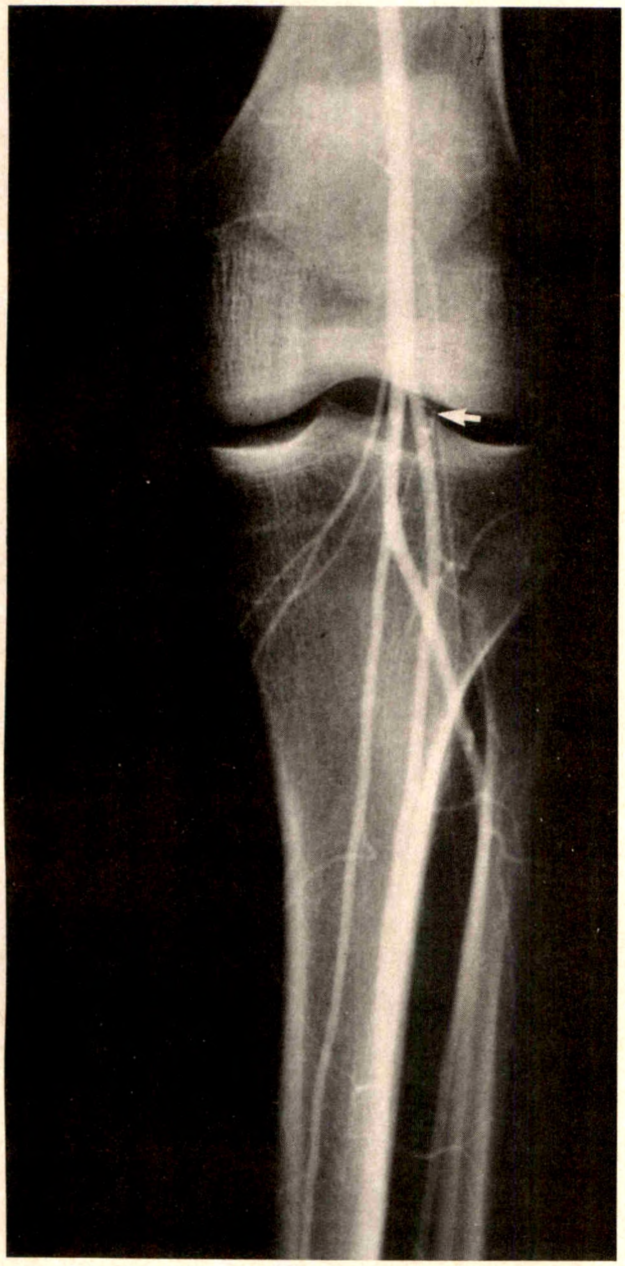

FIG. 8. Type IIC. The peroneal artery arises from the popliteal artery at the knee joint.

or distal PT favor against atherosclerosis. In instances of collateral reconstitution, there will be a transitional tapering at the junction between the PR and the DP or PT.

Type III-A: hypoplastic-absent PT, distal PT replaced to PR. A clinical example of this variation has been detailed above. Bardsley proposed that this variant "represents disappearance of the normally retained distal femoral artery with the sciatica persisting as an enlarged peroneal branch."[4]

Type III-B: hypoplastic-absent AT, DP replaced to PR. Our frequency of 1.6% is the lowest of the reported series (3.0% to 7.1%). Cases of these variants have been reported.[11]

Type III-C: hypoplastic-absent AT and PT, both replaced to PR. In this case, the distal distribution of both vessels is supplied by the PR. We found a single previous report of this variant in the radiologic literature.[12] Senior described it as the Artery Saphena Magna, or the Peronea Magna.[10]

In Keen's study there was no right-left predominance of variants.[8] He did find bilaterality in 27.5% of his variants. These factors were not considered in our study because in too many cases either a single extremity was studied or only one provided adequate opacification of the areas of interest. Trotter demonstrated a slight racial but no sexual variation.[7]

Our statistical findings agree with those of the other angiographic studies.[2,3,4] There appears to be greater variation described in the anatomic studies in comparison to those that analyze angiographic data. Authors of other angiographic studies did not include incidence figures for subtypes we found in Type III, but either grouped them together[2] or included only one of the three types.[3,4] We believe that the completeness offered by our system is justified clinically by the increasing number of distal angioplasties and femorotibial arterial bypass grafts being performed.

Awareness of these popliteal arterial variants is important for those performing surgical or percutaneous vascular reconstruction in the lower extremity. We propose the modification of Lippert's system as a more practical guide to the clinically significant arterial variants in this frequently studied anatomic area.

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Late Failure of Reversed Vein Bypass Grafts

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Late failure of reversed vein bypass grafts is preceded by the appearance of stenotic lesions, which progress to total occlusion. These lesions appear either as intrinsic graft lesions or as new arteriosclerotic lesions in contiguous arteries. The present study summarizes the University of Pennsylvania experience with these lesions in 521 vein grafts inserted from 1979 to 1985. The grafts were grouped according to the site of the distal anastomosis; 231 above-knee popliteal (FP AK), 171 below-knee popliteal (FP BK), and 119 tibial (FT). The overall incidence of stenotic lesions was essentially identical with the three grafts (21%), but the relative incidence of intrinsic graft to arterial lesions was higher with the more distal grafts. The most common graft lesions developed adjacent to the proximal anastomosis, which is the narrowest part of a reversed vein graft. The popliteal artery was the most common site of outflow stenosis. There was negligible incidence of tibial lesions. The most common inflow arterial lesion was located in the common femoral and iliac arteries. The superficial femoral artery (SFA) was a rare site of inflow stenosis, even though it was at risk because 96 grafts originated from the SFA or popliteal artery. Sixty-seven per cent of the graft and 52% of the arterial lesions were treated successfully by percutaneous transluminal angioplasty; the rest had minor surgical revisions. This resulted in a 19%, 10%, and 9% improvement in 5-year patency for the FT, FP BK, and FP AK bypasses. These results justify an aggressive policy of graft surveillance to identify and treat stenotic graft lesions before graft occlusion.

LATE FAILURE OF reversed venous bypass grafts is often preceded by the appearance of stenotic lesions within the graft or contiguous arteries. Detection and treatment of these lesions averts graft occlusion and improves long-term graft patency.

The present study summarizes the results of surgery in 521 reversed vein grafts (*in situ* grafts have specifically been excluded from analysis) in which aggressive follow-up has uncovered a 21% incidence of potentially treatable graft and arterial lesions in above-knee popliteal (FP AK), below-knee popliteal (FP BK), and tibial (FT) grafts. The study emphasizes the importance of early detection of stenotic lesions before graft occlusion to achieve superior long-term graft patency.

Materials and Methods

All infrainguinal reversed vein bypass grafts (521 in all) performed at the Hospital of the University of Pennsylvania between 1979 and 1985 were analyzed retrospectively. The grafts were grouped according to the site of distal anastomosis: 231 FP AK, 171 FP BK, and 119 FT. Forty-four per cent of operations were performed because of threatened limb loss based on symptoms of rest pain or the presence of ischemic lesions (Table 1). The incidence of limb salvage operations varied between grafts and ranged from 79% for FT to 28% for FP AK. Diabetics accounted for 38% (200 of 521 patients) of grafts overall and diabetes was present in 50% of FT grafts (Table 1).

Follow-up examinations included documentation of ischemic symptoms, if any, palpation of peripheral and/or graft pulses, and noninvasive studies, all performed at the time of discharge and at 3-month intervals during the first 18 to 24 months. After 24 months follow-up examinations occurred at 6-month intervals. Vascular laboratory measurements included measurement of segmental arterial pressures and pulse volume recordings (PVR). If the ankle brachial index (ABI) decreased ≥ 0.2 or the PVR amplitude decreased ≥ 5 mm, a presumptive diagnosis of graft failure was made and an arteriogram was ordered, even if the patient was asymptomatic and had satisfactory pulses. The importance of vascular laboratory testing for detection of graft lesions and the parameters used to diagnose the failing graft have been published.[1–4]

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TABLE 1. *Indications for Surgery and Incidence of Diabetes by Graft Type*

	FP-AK		FP-BK		FT		Total	
Grafts	231		171		119		521	
Claudication	166	72%	102	60%	25	21%	293	56%
Limb Salvage	65	28%	69	40%	94	79%	228	44%
Diabetes	78	34%	62	36%	60	50%	200	38%

When the arteriogram revealed stenotic lesions in the graft or contiguous arteries, percutaneous transluminal angioplasty (PTA) was the first treatment choice. We have published details of this technique with respect to vein graft lesions.[5] Alternative surgical methods of treatment include vein patch angioplasty, short bypass grafts around proximal stenotic lesions, and short extension grafts to bypass distal lesions.[6–8]

Life-table patency was calculated according to the guidelines of the Ad Hoc Committee on Reporting Standards for the Society of Vascular Surgery and the International Society of Cardiovascular Surgery.[9] Cumulative patency reported herein includes grafts in which patency was maintained by treating stenotic lesions before graft occlusion. It has been suggested that this be referred to as assisted primary patency[10] to differentiate it from secondary patency, which includes reopened occluded grafts. Primary patencies were also calculated, in which any occlusion or reintervention, no matter how minor, was considered an endpoint for graft patency. Treatment of new inflow or outflow arterial lesions beyond the graft and its two anastomoses did not represent an endpoint with respect to primary patency by these criteria.

Results

Twenty-one per cent (109 of 521 grafts) of grafted limbs developed a stenotic lesion diagnosed on follow-up examination and confirmed by arteriography (Table 2). In 12% (61 of 521 grafts) of bypasses, lesions were localized to the vein graft and in 9% (48 of 521 grafts), lesions were in contiguous inflow or outflow arteries. Although each graft had essentially equal incidences of stenoses, the distribution of these lesions by graft type revealed a progressively higher incidence of graft lesions and lower incidence of arterial lesions with the more distal grafts. As shown in Table 3 the relative percentages of graft/arterial lesions varies from 38 to 62 for FP AK, 58 to 42 FP BK, to 85 to 15 FT. The most common graft lesion was found near the proximal anastomosis and accounted for 56% (34 of 61 graft lesions) of total graft lesions. The proximal anastomosis represents the smallest end of a reversed vein graft and, therefore, it is not surprising that the relative incidence of proximal graft stenosis was highest with the FT grafts.

TABLE 2. *Reversed Vein Bypass Grafts: Location and Incidence of Stenotic Lesions by Graft Type*

	FP-AK		FP-BK		FT		Total	
Grafts No.	231		171		119		521	
Inflow artery	15	6%	10	6%	4	3%	29	5%
Outflow artery	14	6%	5	3%	0	0%	19	4%
Graft conduit	18	8%	21	12%	22	18%	61	12%
Total stenotic grafts	47	20%	36	21%	26	21%	109	21%

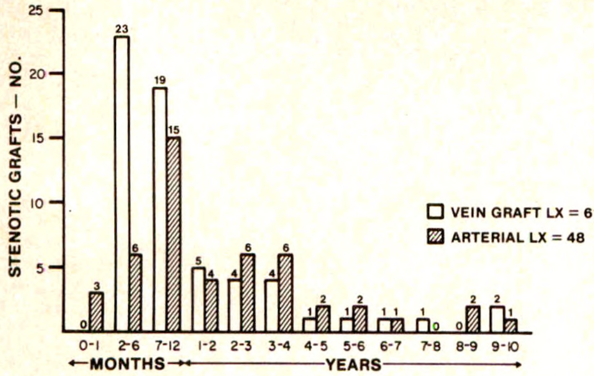
Outflow arterial lesions developed in 4% (19 of 521 bypasses) of grafted limbs. The incidence was 6% (14 of 231 bypasses) in FP AK, 3% (5 of 171 bypasses) in FP BK, and 0% (0 of 119 patients) in FT grafts. The popliteal artery, rather than the more distal vessels, was the predominant site of disease. Some of these lesions developed close to the distal anastomosis and may have been caused by clamp trauma. Others developed at sites distant from the anastomosis and clearly represented progression of atherosclerotic disease.

Inflow arterial lesions appeared in 5% (29 of 521 bypasses) of grafted limbs, predominantly in common femoral or iliac arteries. The superficial femoral artery (SFA) was a rare site of an inflow stenosis, even though 18% (96 of 521 grafts) of grafts were at risk because the proximal anastomosis was located distal to the common femoral artery. Even in the FT grafts, where 39% (46 of 119 grafts) of proximal anastomoses arose from the superficial femoral or popliteal artery, only a single SFA stenosis occurred. This data reinforces the suitability of the more distal SFA or popliteal artery as a proximal site for graft insertion.[11]

The interval from surgery to the appearance of stenotic lesions is shown in Figure 1. The number of arterial and graft lesions are indicated separately at each interval along with the incidence of stenosis, based on the number of grafts at risk at the beginning of each interval. In addition the cumulative stenosis is calculated based on the total number of stenotic grafts (109) observed during the 10 years of follow-up. The majority (61%) of lesions appeared by 1 year. The peak incidence of graft lesions occurred during the first 6 postoperative months, while the arterial lesions peaked 6 months later. Twenty-four per cent (126 of 521 grafts) of grafts occluded during 10 years of follow-up and 60% of these occlusions appeared by 1 year, par-

TABLE 3. *Reversed Vein Bypass Grafts: Distribution of Stenotic Lesions by Graft Type*

	FP-AK		FP-BK		FT		Total	
Arterial	29	62%	15	42%	4	15%	48	44%
Graft	18	38%	21	58%	22	85%	61	56%
Total stenotic grafts	47		36		26		109	

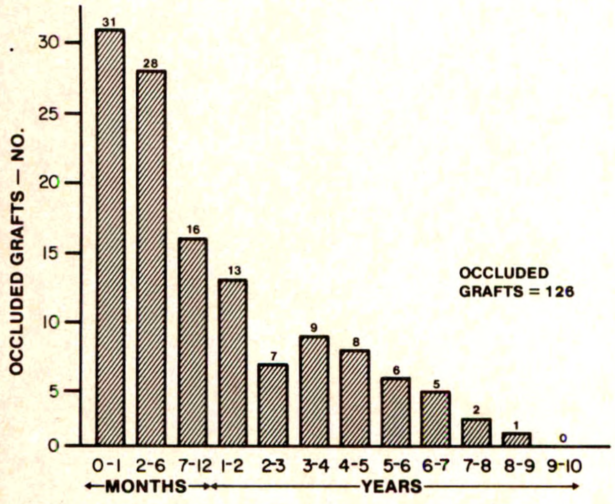


NO GFTS AT RISK	521	447	384	334	255	185	129	71	35	18	16	13
INTERVAL STENOSIS RATE %	5.8	6.5	8.9	2.7	3.9	5.4	2.3	4.2	5.7	5.6	12.5	10.9
CUMULATIVE STENOSIS %	3	29	61	69	78	87	90	93	94	95	97	100

FIG. 1. Appearance time of the stenotic graft conduit and contiguous arterial lesions. Interval stenosis is the percentage of stenosis, based on grafts at risk for each interval. Cumulative stenosis is the percentage of total stenoses observed during 10 years of follow-up (109), which have appeared by each interval.

alleling the 1-year incidence of stenotic grafts. (Fig. 2). The major difference was in the early postoperative interval (0 to 1 month) in which 25% of the occlusions, but only 3% of stenoses, occurred.

PTA was the preferred method of treating graft and arterial lesions and was the initial treatment in 89% (54 of 61 graft lesions) of graft lesions and 60% (29 of 48 arterial lesions) of arterial lesions. Thirty- three per cent (18 of 54 graft lesions) of graft and 17% (5 of 29 arterial lesions) of arterial lesions recurred at least once after PTA. Some recurrent lesions were redilated a second and third time, but ultimately most were corrected surgically. Notwithstanding this, overall, 67% (41 of 61 graft lesions) of graft lesions and 52% (25 of 48 arterial lesions) of arterial lesions were treated by PTA alone.



NO. GFTS AT RISK	521	446	400	361	282	176	147	85	43	25	20	15
INTERVAL OCCLUSION RATE %	5.9	6.3	4.0	3.6	2.5	5.1	5.4	7.1	11.6	8.0	5.0	0.0
CUMULATIVE OCCLUSIONS %	25	47	60	70	75	82	89	94	97	98	100	

FIG. 2. Appearance time of occluded grafts. Interval occlusion rate is the percentage of occlusions, based on grafts at risk for each interval. Cumulative occlusions are the percentage of total occlusion observed during 10 years of follow-up (126), which have appeared by each interval.

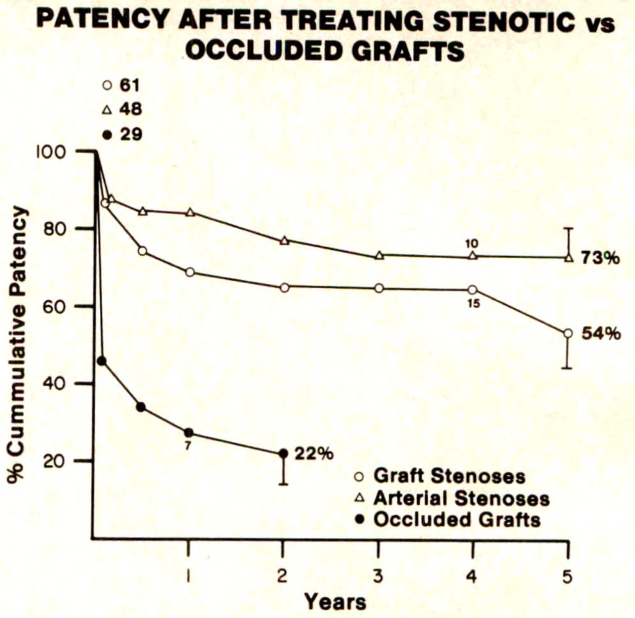


FIG. 3. Cumulative patency achieved after treating stenotic vein grafts, new arterial stenoses, and occluded grafts.

The 5-year cumulative graft patency after the treatment of stenoses was 73% for arterial and 54% for graft lesions (Fig. 3). The treatment of 29 occluded grafts, using thrombectomy and/or thrombolytic therapy, resulted in a meager 22% 2-year patency, emphasizing the importance of diagnosing stenotic lesions before graft occlusion.

Cumulative and primary patencies are shown in Table 4 and Figure 4. The difference between cumulative and primary patency represents the improved graft patency achieved by treating failing grafts and forestalling graft

TABLE 4. *Five-Year Cumulative Patency by Graft Type and Surgical Indication*

	FP-AK (%)	FP-BK (%)	FT (%)
Claudication			
Patency	81*	75	62* (NS)
Primary patency	73	61	48
Salvage			
Patency	68	52*	72* ($p < 0.05$)
Primary patency	51	44	56

* Groups compared for significance of difference.

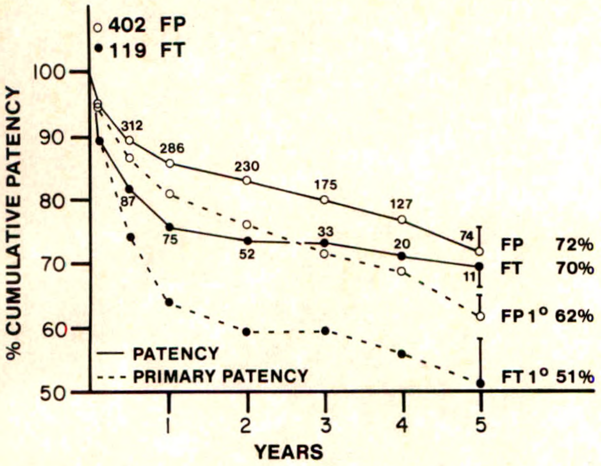


FIG. 4. Cumulative patency of FP and FT vein grafts. These patencies include grafts, in which stenoses, but not occlusions, have been corrected to maintain patency. Primary patencies consider stenoses and occlusions as endpoints for graft patency.

occlusion. The overall improvement in 5-year patency was 10% for FP and 19% for FT grafts (Fig. 4). This relationship held true even when graft patency was analyzed according to indications for surgery (Table 4). An unexpected result was the superior patency of FT grafts done for salvage, especially when compared to the FP BK grafts ($p < 0.05$).

Discussion

Since the classic article on vein graft lesions by Szilagyi,[12] several studies have documented the problem of vein graft and arterial lesions, which are a potential cause of graft failure.[1,2,4,6-8] The present study adds to this data by recording our observations in a large group of venous bypass grafts and emphasizes the relative distribution of graft/arterial lesions as they relate to the most distal level of the grafted artery. Intimal hyperplasia is the major cause of intrinsic graft lesions and is found predominantly near the proximal anastomosis. The higher incidence of this lesion found with tibial grafts suggests an association with the small graft lumen of tibial grafts, compared to FP BK and FP AK grafts. Despite an extensive body of work describing pathologic changes in vein grafts,[13,14] no definitive cause has been identified and no suitable preventative strategies have been developed. In the present series, many, but not all, patients have been treated with antiplatelet drugs, including aspirin and dipyridamole before operation and in the postoperative period. While we believe that this has contributed to lower perioperative graft occlusions, there is no evidence that it has reduced the incidence of vein graft lesions.

Arteriosclerotic disease in adjacent arteries predisposes these vessels to clamp trauma during the performance of bypass surgery. This may account for those lesions seen in juxtaposition to the proximal or distal anastomosis, but does not explain the development of new lesions at a distance from the anastomotic areas.

The present study confirms previous reports that these lesions appear early,[1,4,6] with 61% of stenoses appearing by 1 year and 78% of stenoses appearing by 3 years. Interestingly these cumulative rates of graft stenoses parallel graft occlusions after the initial postoperative period, where technical factors are the predominant cause for graft occlusion.[6,15] This data reinforces the need for frequent follow-up evaluation during the first 1 to 2 postoperative years to detect stenotic lesions before graft occlusion.

Comparison of the patency rate achieved in the present series of bypass grafts with previous reports from our institution in 1978[16,17] indicate that a significant improvement in graft patency has occurred with femoropopliteal bypass grafts. For claudicators the 5-year patency has improved from 68%[16] to 75% and 81%, and for the salvage group from 46%[17] to 52% and 68% (Table 4), depending on whether the distal anastomosis was in the AK or BK popliteal artery. Superior contemporary patency rates have also been reported by others for femoropopliteal grafts.[18-20] Recent reports of femorotibial grafts also show higher patency,[21-24] compared to older reports.[25-27]

While improved technical refinements have certainly produced part of this improvement, we believe that the detection and treatment of stenotic lesions have had a major impact on graft patency in our series. Several other investigators have reported data similiar to our own, with a high incidence of graft lesions detected in the postoperative period,[2,6-8] while others have not. We have no explanation as to why the recent report of Taylor[21] on tibial grafts does not indicate any significant appearance of these late stenotic lesions and we are tantalized by their excellent primary patency rates, despite the fact that the technical details of their operations are similar to our own methods. Perhaps part of the discrepancy may be related to the shorter follow-up period because only 10 of 110 tibial grafts were available for follow-up at 3 years. In contrast to this, however, is the fact that a majority of stenotic lesions should have appeared within this 3-year interval.

Our data also varies somewhat with other reported studies of femoropopliteal grafts in which FP BK bypass grafts have been associated with a higher patency rate than the FP AK grafts.[19,28] This has been attributed to bypassing potential areas of stenosis in the popliteal artery with the BK grafts. While this is a reasonable assumption, the present data do not support it. No significant differences in patency were observed in FP BK *versus* FP AK grafts, regardless of the indication for surgery. However for the limb salvage group, FT patency was significantly better than FP BK, which suggests that the tibial vessels are the preferred site of distal anastomosis when operating for limb salvage.

Our data indicate that bypass to more distal vessels is associated with the development of more intrinsic vein graft lesions and fewer new arterial lesions. We have demonstrated that both types of lesions can be corrected by PTA or surgery, but that PTA continues to be our primary method of therapy. Veith[2] has also used PTA as primary treatment for graft lesions, while others[6–8] have preferred to treat these lesions surgically.

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Ultrasonic Mucosal Proctectomy in Patients with Ulcerative Colitis

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A technique for performing mucosal proctectomy in patients with ulcerative colitis using ultrasonic fragmentation is described. Twenty-eight patients undergoing colectomy and ileoanal anastomosis were studied. Removal of the mucosal layer of the distal rectum was performed using a titanium probe vibrating at 23 kHZ with an amplitude of 300 microns. This method produces complete mucosal destruction and the resulting debris and irrigating fluid is removed through the hollow central portion of the probe. Healing of the ileoanal anastomosis does not appear to be adversely affected by the use of this technique. Because ultrasonic fragmentation is not dependent on the integrity of the submucosal plane, it may be advantageous in those cases in which severe inflammation and submucosal scarring make manual dissection of the rectal mucosa difficult to perform.

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TOTAL COLECTOMY WITH mucosal proctectomy and ileoanal anastomosis is now the operation of choice for most patients with ulcerative colitis. Ileoanal anastomosis was described by Ravitch and Sabiston[1] in 1947, but this procedure was not used extensively until 30 years later when Martin and others[2] demonstrated that good results could be obtained in patients with ulcerative colitis. The technique for performing the mucosal proctectomy has required modification as more patients with severe ulcerative colitis have become candidates for this operation. Initial efforts to remove the mucosa of the entire rectum[3] were subsequently abandoned in favor of a short stripped segment with performance of the dissection from the perineal approach. This change became necessary in part due to the difficulties caused by severe mucosal inflammation and submucosal scarring.[4] Although the operation can now be performed with a relatively low rate of morbidity, problems related to manual separation of the mucosal layer from the underlying muscularis still remain. In difficult cases incomplete mucosal dissection can lead to residual microscopic islands of retained mucosa with a malignant potential.[5,6] Also when the plane of dissection is obliterated, damage to the sphincter muscles and rectovaginal fistulae may result.[7] To avoid some of these problems, a new technique for mucosal proctectomy has been developed in which ultrasonic fragmentation is used to destroy the mucosal layer. Previous work using animal models has demonstrated that this method is capable of reliably removing the rectal mucosa with preservation of the underlying muscularis.[8–10] The present study was performed to determine the applicability of this technique in patients with ulcerative colitis.

Clinical Material and Methods

Twenty-eight patients with ulcerative colitis undergoing ileoanal anastomosis had mucosal proctectomy performed using ultrasonic fragmentation. They ranged in age from 17 to 62 years, with a mean of 30 years. The mean duration of symptoms before operation was 6 years (range, 6 months to 24 years). Twelve patients were female and 16 were male. Twenty-three patients were operated on for severe symptoms that were unresponsive to intensive medical therapy. The remaining five patients required surgery for premalignant changes. Six patients underwent total colectomy, mucosal proctectomy, and ileoanal anastomosis in one stage, while 22 patients had a preliminary subtotal colectomy and ileostomy followed by mucosal proctectomy and ileoanal anastomosis 3 to 6 months later. Patients with severe rectal bleeding, malnutrition, and steroid toxicity underwent a staged procedure.

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Surgical Technique

Removal of the mucosal layer is carried out using ultrasonic fragmentation with a titanium probe vibrating at 23 kHZ (CUSA NS-100, Cavitron, Inc., Stamford, Connecticut). No attempt is made to develop the submucosal plane and elevate the mucosa. Epinephrine solution is not used. The mucosa is exposed using a selfretaining Sims rectal retractor with 12-cm blades. The ultrasonic probe is held at an angle of approximately 30 degrees and the dissection of the rectal wall starts at the dentate line. The instrument is set at full power, which provides an amplitude of vibration of about 300 μm. Touching the tip of the ultrasonic probe to the mucosal layer at these settings causes immediate mucosal destruction. The fragmented mucosal cells are removed by suction through the central hollow portion of the probe. Constant irrigation provides cooling and aids in the removal of the resulting debris. The entire mucosal layer is exposed to the ultrasonic probe systematically and repeatedly by dividing the rectum into four equal quadrants and destroying the mucosa in each quadrant for a distance of 7 cm from the dentate line. This is best accomplished by constantly moving the probe mostly in the transverse plane. The mucosal proctectomy is complete when the circular muscle fibers are clearly visible. When necessary hemostasis is achieved using the electrocautery. To confirm the depth of dissection, four biopsies are obtained at the completion of the procedure and sent for frozen section.

Colectomy and resection of the proximal rectum is performed synchronously by the abdominal operating team. The rectum is dissected to the level of the levator muscles where it is transected, leaving a cuff of stripped rectal muscularis 3 to 4 cm long. The neorectum was fashioned using a J-pouch ileoanal anastomosis in 25 patients. In the remaining three patients, a straight ileoanal anastomosis was used. All patients had a temporary ileostomy performed.

Results

Mucosal proctectomy was performed in the prone jackknife position at the beginning of the operation in the first 14 patients. Thereafter mucosal stripping was performed in the lithotomy position after abdominal exploration. The mean duration of ultrasonic fragmentation needed to remove the rectal mucosa for a distance of 7 cm in the first 13 patients was 15.3 minutes (range, 11.8–18.7 minutes). This was accomplished using the standard NS-100 CUSA tip. A new tip (part number SK2879, Cavitron, Inc. Stamford, CT.) with a distal diameter increase of 25% was subsequently used (Table 1). This probe diminished the duration of ultrasonic fragmentation to a

TABLE 1. *Ultrasonic Mucosal Proctectomy: Clinical Material*

ID	Age	Sex	Duration of Symptoms (Years)	Severity of Rectal Inflammation	Previous Colectomy	Duration of Ultrasonic Fragmentation	Type of Pouch	Postoperative Stay (Days)	Closure of Ileostomy (Months)
1	23	F	3	Moderate	Yes	14	J-pouch	16	3
2	34	M	18	Moderate	No	11.8	J-pouch	18	3
3	39	M	10	Severe	No	14.7	J-pouch	15	2
4	40	F	2	Moderate	Yes	16.4	J-pouch	17	2
5	18	M	3	Severe	Yes	17.7	J-pouch	15	2
6	27	F	5	Severe	Yes	18.7	None	15	4
7	22	M	1	Moderate	Yes	18.7	J-pouch	12	4
8	21	M	1	Severe	Yes	15.9	J-pouch	10	3
9	18	M	1	Severe	Yes	12	J-pouch	12	3
10	23	M	1	Severe	Yes	16.2	J-pouch	11	16
11	17	M	1	Severe	Yes	12.3	None	11	7
12	27	F	3	Moderate	Yes	15.7	J-pouch	11	2
13	28	M	0.5	Severe	Yes	15	J-pouch	10	2
14	23	F	3	Severe	Yes	7.3	J-pouch	11	3
15	36	F	11	Severe	No	10	J-pouch	8	5
16	23	M	2	Severe	Yes	9.6	J-pouch	9	2
17	62	F	4	Severe	Yes	10.2	J-pouch	11	4
18	31	F	1	Severe	Yes	13	J-pouch	12	3
19	32	F	3	Severe	Yes	10	J-pouch	11	3
20	21	M	1	Moderate	Yes	10.8	None	10	6
21	19	F	1	Moderate	Yes	10	J-pouch	20	4
22	32	F	3	Severe	Yes	8.7	J-pouch	9	2
23	41	M	24	Mild	No	11.3	J-pouch	13	4
24	41	M	22	Mild	No	7.7	J-pouch	21	9
25	35	M	12	Moderate	No	10.3	J-pouch	17	3
26	32	F	3	Moderate	Yes	10.4	J-pouch	10	3
27	46	M	16	Moderate	Yes	11.4	J-pouch	10	3
28	34	M	6	Severe	Yes	14.1	J-pouch	8	3

mean of 10.3 minutes (range, 7.3–14.1 minutes). The estimated mean blood loss during mucosal proctectomy was 511 mL.

Examination of the 108 biopsy samples obtained at the completion of the mucosal proctectomy revealed absence of any residual mucosa in 107 samples. Only one biopsy sample of the anterior rectal wall obtained from the third patient in this series showed a few islands of recognizable mucosal glands. Ultrasonic fragmentation was continued for an additional two minutes and repeat biopsies were then negative. Study of the tissue removed by ultrasonic fragmentation showed an amorphous mass of cellular debris with only an occasional island of nondisrupted mucosal cells (Fig. 1).

The mean postoperative stay for the entire group of patients was 12 days (range, 8 to 21 days). Surgical revision of the anastomosis was necessary in one patient who developed a partial separation of a straight ileoanal anastomosis. Another patient with a J-pouch ileoanal anastomosis developed an internal sinus that did not heal after 6 months of observation and was treated by marsupialization. Two patients developed a stricture of the anastomosis that was sufficiently severe to require dilatation under anesthesia. Pelvic sepsis manifested by purulent drainage from the pelvic drains occurred in two patients and resolved with antibiotics. Only one patient required a laparotomy in the early postoperative period that was performed to relieve a partial intestinal obstruction caused by adhesions adjacent to the loop ileostomy (Table 2).

TABLE 2. *Complications*

Complication	Number	Treatment
A. Immediate Postoperative Period		
Pelvic sepsis	2	Antibiotics
Hemorrhage from pouch suture line	1	Suture of bleeding vessel
Partial dehiscence of anastomosis	1	Secondary suture
Small bowel obstruction	1	Lysis of adhesions
Temporary peroneal nerve palsy	1	Observation
B. Delayed Complications		
Stricture	2	Dilatation
Vulvar cellulitis	1	Antibiotics
Internal sinus	1	Marsupialization
Stool frequency	1	Ileostomy

The anastomosis eventually healed well in all patients. The mean duration from the initial operation to closure of the ileostomy was 3.9 months (range, 2–16 months). Only three patients had a delay in closure of the ileostomy of more than 6 months.

Functional Results

Twenty-three patients have been followed for at least 6 months after closure of ileostomy. Twenty have a J-pouch ileoanal anastomosis and three have a straight ileoanal anastomosis. All patients can evacuate spontaneously and none have frank incontinence. The mean number of bowel movements is 5.7 per 24 hours, with a

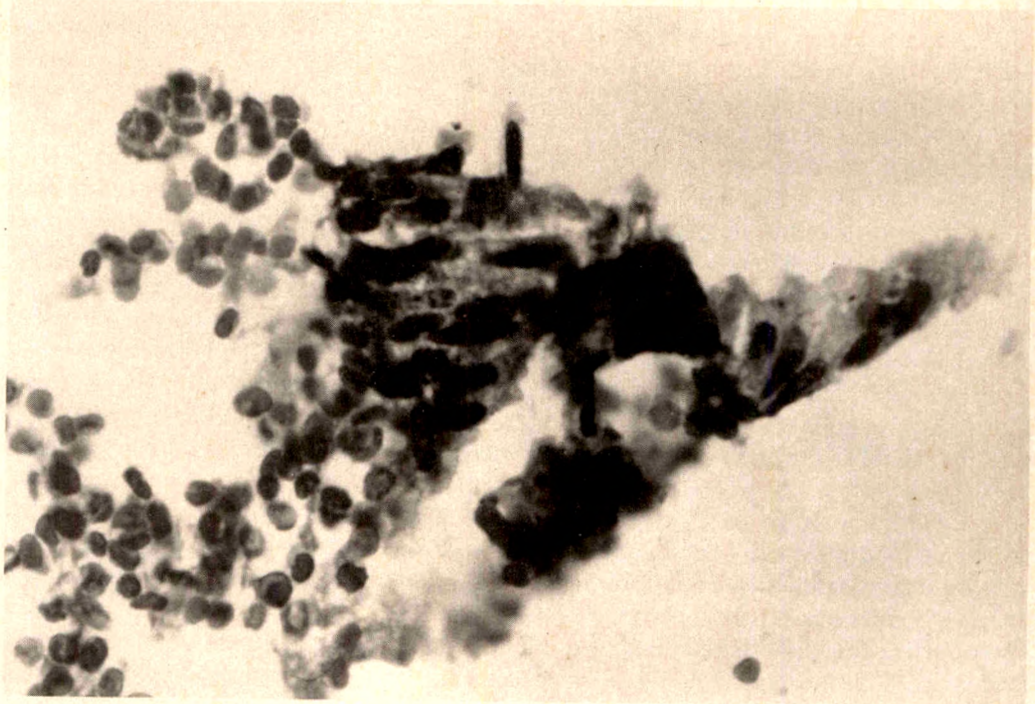

FIG. 1. Cell block containing mucosal debris aspirated during ultrasonic mucosal protectomy in a patient with ulcerative colitis. An aggregate formed by several columnar mucosal cells and erythrocytes is present (hematoxylin and eosin × 400).

mean duration of follow up of 18 months. Thirteen patients do not require any antidiarrheal medication. A small amount of seepage of fluid, usually at night, is present intermittently in nine patients. One of the patients with a straight ileoanal anastomosis subsequently required an ileostomy 2 years later because of frequency of bowel movements. The other two are doing well and the frequency of bowel movements is similar to that of the patients with a J-pouch.

Discussion

The ideal technique for mucosal proctectomy should allow complete removal of the mucosal layer with preservation of the surrounding musculature. Excision of the mucosa can be performed manually with relative ease in the normal rectum and in patients with polyposis coli who have not had fulguration of polyps. In ulcerative colitis, as the disease progresses, mucosal separation becomes more difficult. Although in the majority of patients with ulcerative colitis manual separation of the mucosal layer can be performed in the short segment required for an ileoanal anastomosis, sometimes cases are encountered in which even experienced surgeons cannot perform a manual dissection. In these situations the operation has either been abandoned and an abdominoperineal resection performed, or a curette has been used to scrape the mucosa from the underlying layers.[11-13] Although the use of mucosal curettage results in a partially denuded base for the ileoanal anastomosis, it does not provide uniform depth of dissection and therefore complete mucosal excision is difficult to achieve.

A far more common problem occurs in the patient with severe ulcerative colitis in whom manual mucosal proctectomy can be performed only with difficulty. O'Connell and others[6] demonstrated that residual islands of mucosa were present in the rectal muscle cuff of 14% of the patients in whom the ileoanal reservoir was examined after excision. It is likely that these remnants result from deviation of the plane of manual dissection. Because the potential for malignant transformation in ulcerative colitis is significant, it appears that changes in surgical technique may become necessary to avoid this problem. Another problem associated with difficult mucosal dissections in women with ulcerative colitis is that injury to the rectovaginal septum may result in vaginal perforation and rectovaginal fistula.[14]

To avoid some of the problems previously described, several alternate methods of dissection have been reported that may have potential use in performing mucosal proctectomy. Studies using chemical debridement for removal of the rectal mucosa have been described in the canine model.[15,16] With this technique repeated applications of sodium hydroxide solution are required over several days to produce sloughing of the mucosal layer. Because multiple applications are necessary it is unlikely that chemical debridement will become useful in a clinical setting. Another method using mucosal photosensitization followed by exposure to a controlled amount of laser light recently has been reported in rats.[17] This new technique appears to be promising but careful control of the amount of light exposure is necessary to avoid intestinal perforation. Also because the entire patient is photosensitized, exposure of the abdominal contents to light during the operative procedure may have potentially deleterious effects.

Our experience with ultrasonic fragmentation shows that with meticulous technique removal of the mucosa of the distal rectum is possible even in patients with severe inflammation and submucosal scarring. Because the depth of dissection is proportional to the duration of exposure to the ultrasonic probe, there is more control than in cases in which manual separation is difficult. Continence does not appear to be affected by the use of ultrasonic fragmentation. The number of bowel movements and incidence of nocturnal seepage of stool is similar to that reported in large series in which mucosal proctectomy was performed manually.[18]

The incidence of surgical complications in this study was also similar to that reported by other institutions.[18-20] There were no complications that could be attributed directly to the use of the ultrasonic probe such as perforation of the rectal wall. Healing of the ileoanal anastomosis does not seem to be adversely affected by the use of ultrasonic fragmentation, and closure of the temporary ileostomy was possible within 4 months in 82% of patients. One of the potential advantages of using ultrasonic fragmentation for mucosal proctectomy in patients with severe ulcerative colitis is the possibility of a lower likelihood of leaving viable islands of mucosa than after a difficult manual mucosal proctectomy. Only one of the 108 biopsies taken after ultrasonic mucosal proctectomy showed identifiable residual mucosa. This occurred early in this series, and after further ultrasonic fragmentation the repeat biopsies were negative.

Patients with severe mucosal destruction and submucosal scarring may be the best candidates for this technique because the thin residual mucosa is easily destroyed and the scarred submucosa provides a protective barrier for the surrounding muscle layer. Although it is preferable to perform the entire mucosal proctectomy using one technique, it is likely that ultrasonic fragmentation also may be useful after a difficult manual dissection. Provided that the bed of rectal circular muscle is sufficiently intact, ultrasonic fragmentation can be used to destroy any residual islands of mucosa. Under these circumstances, a much shorter duration of exposure would be necessary.

Ultrasonic mucosal proctectomy can be safely performed in patients with severe ulcerative colitis and can lead to excellent functional results. This technique may be of particular benefit in those patients in whom manual dissection is difficult to perform. Ultrasonic fragmentation appears to be useful either as the primary technique for mucosal proctectomy in difficult cases, or as an adjunct to manual dissection to decrease the incidence of residual mucosa.

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Prognostic Significance of DNA Content Abnormalities in Young Patients with Colorectal Cancer

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Several studies have shown that the presence of DNA ploidy abnormalities, measured by flow cytometry, may correlate with a poor prognosis in a variety of cancers. The predictive value of these DNA abnormalities in young patients with colorectal cancer has not been well studied. Fifty patients aged 40 years and younger with colorectal adenocarcinoma were studied to determine the correlation of tumor DNA abnormalities with survival. DNA content was determined by flow cytometric analysis and each tumor was categorized as diploid or nondiploid. Of the parameters studied, Dukes' classification and tumor DNA ploidy were found to be significant prognostic indicators. Determination of DNA content seems to provide additional useful prognostic information in young patients with colorectal cancer.

COLORECTAL CANCER USUALLY occurs in older patients. When it presents in young patients it is often associated with conditions such as multiple polyposis and ulcerative colitis.[1,2] Occasionally, however, colorectal cancer occurs in patients younger than 40 years without any obvious predisposing cause.[3,4] These young patients frequently have advanced disease at the time of diagnosis, and therefore a poor prognosis. It is unclear whether this poor prognosis is related to tumor aggressiveness or merely to delay in diagnosis and therefore a greater likelihood that the cancer will be discovered at a more advanced stage.[5,6] DNA content abnormalities have recently been associated with a poor prognosis in colorectal and other cancers.[7-9] This study was performed to determine the incidence of tumor aneuploidy and its correlation with other prognostic indicators and survival in a group of patients age 40 years or less with colorectal cancer in the absence of ulcerative colitis or multiple polyposis.

Materials and Methods

Fifty young patients with colorectal adenocarcinoma undergoing surgical treatment at The Mount Sinai Hospital in New York between 1968 and 1985 were studied retrospectively. All patients were 40 years of age or younger at the time of admission to the hospital. The mean age was 34 with a range from 25 to 40 years. Patients with inflammatory bowel disease or multiple polyposis coli were excluded. Clinical information obtained from each patient included sex, age, location of the tumor, type of operation performed, family history of colorectal and noncolorectal cancer, and incidence of second cancers. Follow-up information was obtained by direct patient contact, review of medical records, tumor registry information, or contact with primary physicians. The overall mean duration of follow-up was 52 months.

The method of preparing nuclei from formalin-fixed, paraffin-embedded specimens for analysis by flow cytometry was described by Hedley et al.[8,10] Forty-micron sections of the tumor were dewaxed in xylene. They were then rehydrated in a sequence of washes with decreasing concentrations of ethanol followed by distilled water. The samples were then digested for 60 minutes at 37 C in 0.5% pepsin in normal saline solution acidified to pH of 1.5. The nuclei were then washed three times with phosphate buffered saline. After the last centrifugation, the pellet was stained with propidium iodide in a concentration of 50 μg per milliliter and strained through a 37-μm nylon mesh filter.

The nuclear DNA ploidy pattern was determined on a FACStar flow cytometer (Becton Dickinson, Sunnyvale,

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CA). A minimum of 10,000 events were counted for each sample. All tumor samples contained some inflammatory and stromal cells, which provided an internal diploid standard. The mean coefficient of variation for the $G_{0,1}$ peak was 8.4, with a standard deviation of 1.5. The DNA index was defined as the ratio of the mode of the aneuploid peak divided by the mode of the diploid $G_{0,1}$ peak. Tumors with a distinct peak having a DNA index between 1.1 and 1.9, or greater than 2.1, and containing at least 10% of the nuclei were considered aneuploid. Tetraploid tumors had a second peak corresponding to the location of the $G_2 + M$ peak containing more than 15% of the total number of cells.[11] Nondiploid tumors were defined as those that were either aneuploid or tetraploid.

Adjacent 5-μm sections were stained with hematoxylin and eosin. These sections were examined by one pathologist to determine tumor differentiation and the presence of colloid and signet ring cells. Tumor differentiation was determined according to the classification described by Banner et al.[12] Tumors infiltrating into the submucosa were considered to be Dukes' A, those invading the deeper layers of the bowel wall to the pericolonic serosal fat without lymph node involvement were regarded as Dukes' B, tumors with metastasis to regional lymph nodes were defined as Dukes' C, and those with distant metastasis at the time of operation were classified as Dukes' D.

The data obtained were analyzed using the computer system of the City University of New York. The SAS statistical analysis system (SAS Institute, Inc. Raleigh, NC) was used to compare numeric variables using Student's t test and the Fisher exact test was used for variables grouped into categories. Survival analysis was performed using the BMDP Statistical Software. Actuarial life-table statistics and the Mantel-Cox method were used for comparison of the survival curves. The Cox proportional hazards model using stepwise regression was used for survival analysis with multiple variables.

Results

Of the 50 patients studied, 20 (40%) were men and 30 (60%) were women. Seven patients (14%) were younger than 30 years, 24 (48%) ranged in age from 30 to 35 years, and 19 (38%) were older than 35 years. None of the patients studied had Dukes' A lesions, 17 (34%) had Dukes' B tumors, another 17 (34%) had Dukes' C, and 16 patients (32%) had distant metastasis at operation. In 29 patients (58%) the tumor was well differentiated, in 12 (24%) moderately differentiated, and in 9 (18%) poorly differentiated. Twenty patients (40%) had cancers with colloid features and three tumors (6%) contained signet ring cells. Thirty-five cancers (70%) were located in the rectum or sigmoid colon and the remaining 15 tumors (30%) were distributed throughout the colon. A positive family history of cancer was elicited in 19 patients (38%). Twelve of these (24%) had a history of colorectal cancer in a first-degree relative. The others had a variety of noncolonic cancers. Five patients (10%) had multiple cancers. Two were synchronous colonic cancers and the other three were metachronous noncolonic tumors (uterus and melanoma).

Twenty-six patients (52%) had diploid lesions, 21 (42%) had aneuploid tumors, and 3 (6%) had tetraploid tumors. No association was found between age, sex, location, type of operation, and the DNA ploidy pattern of the carcinoma. The mean DNA index for nondiploid tumors was 1.78. The aneuploid and tetraploid peaks contained a mean of 35% (range, 16% to 75%) of the total number of events counted. There was a correlation between the Dukes classification and the frequency of nondiploid tumors. Of the 16 Dukes' D lesions, ten (63%) were nondiploid. Eight (47%) of the 17 Dukes' C lesions were nondiploid, and only six (35%) of the 17 Dukes' B lesions were nondiploid. The degree of tumor differentiation and presence of colloid did not show a significant correlation with DNA content. Of the 20 colloid cancers, 11 were diploid and 9 were nondiploid.

Forty-one patients had well to moderately differentiated tumors. Twenty-one of these were diploid and 20 were nondiploid. Poorly differentiated tumors were also equally distributed between diploid and nondiploid (five and four, respectively). All three tumors containing signet ring cells were nondiploid. The location of the cancer did not correlate with the incidence of DNA content abnormalities. Fifty per cent of the 28 tumors located in the rectum and rectosigmoid were nondiploid (Fig. 1). There was no significant difference in the incidence of nondiploid tumors in patients with a positive family history of cancer and in those who did not. Patients developing multiple colonic and noncolonic cancers did not have a greater incidence of nondiploid lesions.

The actuarial 5-year survival rate in this series was 53%. Patients with Dukes' B lesions had an 88% 5-year survival rate as opposed to 67% for those with Dukes' C cancers. None of the patients with Dukes' D tumors survived beyond 45 months (Fig. 2). Patients with a positive family history for colorectal and other cancers had a prognosis similar to those without first degree relatives with cancer. The prognosis for patients with colloid and noncolloid lesions was nearly identical. There was no difference in the 5-year survival rates between patients with well- or moderately differentiated tumors. Patients with poorly differentiated tumors had a significantly worse outcome ($p<0.05$, Fig. 3). Comparison of patients with moderate-to-well differentiated tumors by DNA content showed a statistically significant improvement in 5-year survival for diploid tumors of 75% versus 45% for nondiploid lesions

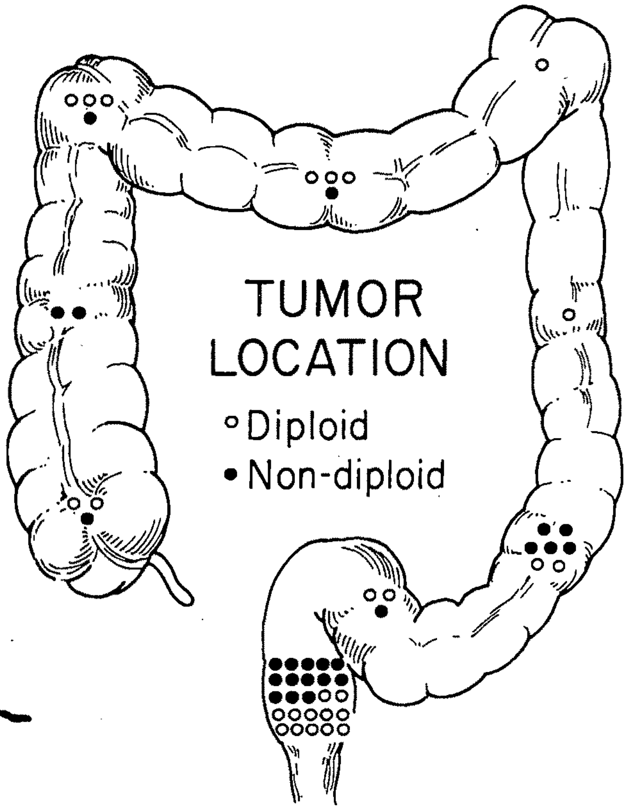

FIG. 1. Location of the cancer in this group of young patients. Seventy per cent of the tumors were located in the rectum and sigmoid colon. There is no correlation between tumor location and DNA content.

($p<0.05$, Fig. 4). Patients with poorly differentiated tumors had a bad prognosis regardless of the DNA content. There was no correlation between DNA index or size of the nondiploid peak and survival.

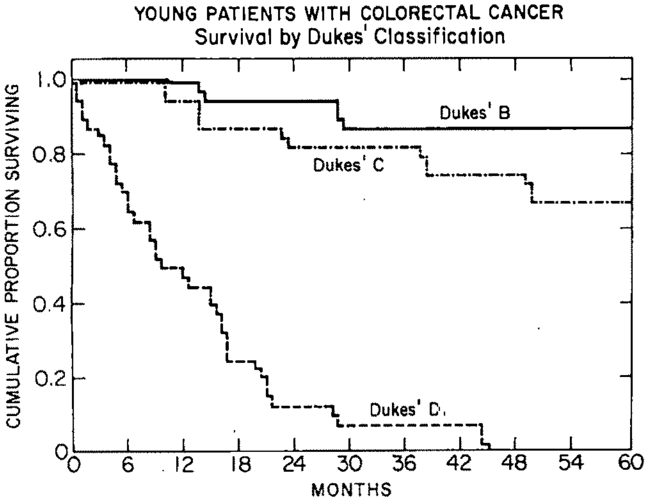

FIG. 2. Actuarial survival curves by Dukes' classification. There were no Dukes' A lesions in this series. The differences are statistically significant ($p<0.001$, Breslow and Savage).

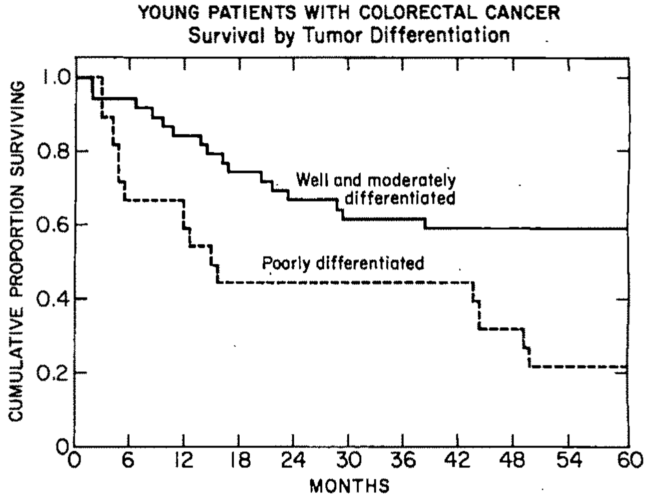

FIG. 3. Comparison of actuarial survival curves for well- and moderately differentiated *versus* poorly differentiated tumors. There is a nearly 40% difference in survival rate at 4 years. ($p<0.05$, Breslow and Savage).

Discussion

Colorectal cancer in young patients has some distinctive features when compared to colorectal cancer in the older population. The incidence of colloid lesions is higher, and there seems to be a greater tendency to have more advanced tumors at diagnosis.[13-15] Forty per cent of the patients studied here had colloid-producing tumors. Follow-up, however, showed that presence of colloid does not correlate with survival. A more important factor accounting for poor prognosis in this series is the high incidence of patients with advanced lesions manifested by the presence of either nodal or distant metastasis at operation.

Approximately 50% of the tumors studied in this group of young patients were nondiploid. This incidence is sim-

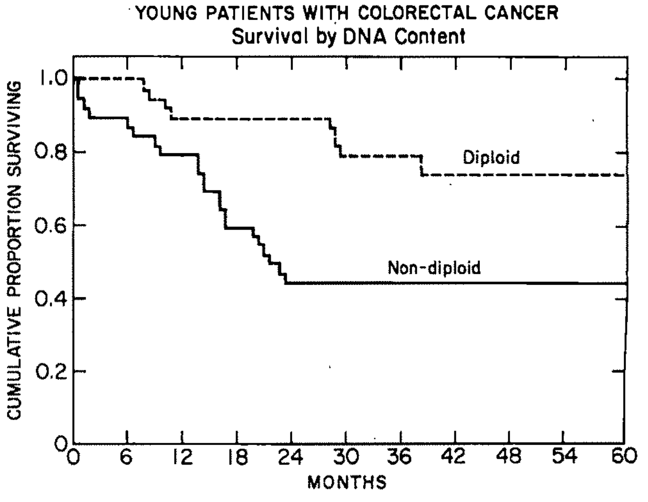

FIG. 4. Survival curves for well- and moderately differentiated cancers by DNA content. Nondiploid tumors have a significantly higher early mortality rate when compared to diploid tumors. ($p<0.05$, Breslow and Savage).

ilar to that reported by Scott in the general population.[16,17] In the present study, there is a significant correlation between advanced Dukes' stage and incidence of DNA ploidy abnormalities. The increased percentage of nondiploid tumors among more advanced lesions has also been observed by Kokal and others[18,19] in older patients. In the present series, nondiploid tumors were not recognizable by standard histologic criteria. There was a lack of correlation between histologic grading or colloid production and DNA content that has been confirmed by Rognum and Emdin.[20,21] Only the presence of signet ring cells in three patients was found to correlate with DNA ploidy abnormality.

The Dukes classification was the best predictor of survival in this study. Tumor differentiation alone was less significant in predicting prognosis than the Dukes classification or DNA content. Eighty per cent of the patients had tumors that were moderately to well differentiated. Within this group diploid tumors had a significantly better prognosis than nondiploid tumors. These results are comparable to those of Emdin, Wolley, and Armitage.[21-23] Patients with poorly differentiated diploid or nondiploid lesions, on the other hand, had a prognosis similar to those with nondiploid moderately to well-differentiated tumors.

One of the major advantages of determination of DNA ploidy is that this information can be obtained from an endoscopic biopsy sample.[24] Preoperative knowledge of DNA ploidy abnormalities may be particularly important for physicians treating patients with rectal cancer (50% of this patient population). All nondiploid rectal cancers were deeply infiltrating and nearly 80% percent of the patients had nodal or distant metastasis. Therefore it is possible that preoperative radiotherapy may be beneficial in selected patients in this group who are likely to have advanced local disease.

Patients developing colorectal cancer when they are younger than 40 years do not appear to have more aggressive tumors as determined by the incidence of DNA content abnormalities and histologic grading of the lesions. Nearly one third of the patients in this study, however, had distant metastasis at the time of diagnosis, and there were no Dukes' A tumors. On the other hand, the prognosis for patients with Dukes' B and C lesions appears to be at least as good as that of the older population. Diagnosis of colorectal cancer in young patients at an earlier stage is a critical factor in improving prognosis. Better understanding of the processes that lead to early cancer formation in this group is necessary to identify individuals who are at high risk.

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Pulmonary Edema After Aneurysm Surgery Is Modified by Mannitol

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Abdominal aortic aneurysmectomy (AAA) results in thromboxane (Tx)A_2 generation, a rise in mean pulmonary artery pressure (MPAP), leukopenia, and noncardiogenic pulmonary edema. This study tests whether mannitol, a hydroxyl radical scavenger, modifies these events. Patients received mannitol 0.2 g/kg (n = 14) or saline (n = 12) intravenously before infrarenal aortic clamping. With saline, 30 minutes after clamping, plasma TxB_2 levels rose from 124 to 290 pg/mL ($p < 0.01$), and MPAP rose from 19 to 27 mmHg ($p < 0.01$). Aortic clamp release led to further increases in plasma TxB_2 to 378 pg/mL ($p < 0.01$) and MPAP to 34 mmHg ($p < 0.01$). The white blood count (WBC) fell from 9800 to 4400/mm^3 ($p < 0.01$). Four to eight hours after surgery, physiologic shunting ($\dot{Q}$[sc]S[xsc]/$\dot{Q}$[sc]T[xsc]) rose from 9% to 20% ($p < 0.01$) and peak inspiratory pressure (PIP) increased from 22 to 32 cmH_2O ($p < 0.01$). Chest radiography demonstrated pulmonary edema while the pulmonary wedge pressure was 12 mmHg, excluding left ventricular failure. By 24 hours pulmonary edema resolved and the PIP and P_aO_2 returned to baseline. Mannitol treatment relative to saline, during and after aortic clamping reduced plasma TxB_2 levels to 155 and 198 pg/mL, respectively ($p < 0.01$); MPAP to 21 and 26 mmHg ($p < 0.01$); minimized the decline in WBC to 5850/mm^3 ($p < 0.01$), and the postoperative rise in $\dot{Q}$[sc]S[xsc]/$\dot{Q}$[sc]T[xsc] to 12%, and PIP to 28 cmH_2O (both $p < 0.01$). Chest radiography showed no pulmonary edema. Finally *in vitro* studies documented that mannitol 1 to 10^{-4}M, but not dextrose, in a dose-dependent manner inhibited Tx synthesis by ADP-activated platelets. These data indicate that mannitol maintains pulmonary function after AAA by limiting ischemia-induced thromboxane synthesis.

REPERFUSION OF ISCHEMIC tissue during abdominal aortic aneurysmectomy (AAA) results in thromboxane (Tx) generation with subsequent pulmonary hypertension and later nonhydrostatic or increased permeability pulmonary edema.[1] Studies in experimental animals have demonstrated that this ischemia-induced lung injury is dependent, in large part, on Tx and neutrophils.[2-4] Thromboxane is an important mediator of this event because inhibition of Tx synthesis or the blockade of Tx receptors[3] prevents pulmonary edema. Although cyclooxygenase inhibitors will limit Tx synthesis and may prevent the lung injury, their clinical application is limited because of the potential of these drugs to aggravate renal failure.[5]

Current evidence also suggests that other potentially toxic agents, such as oxygen-free radicals (OFR), are generated on ischemia and reperfusion.[6] Thus a number of studies document the protective effect of free-radical antagonists and scavengers not only in limiting the local injury after myocardial, intestinal, or renal ischemia[7-9] but also in limiting the pulmonary injury following lower torso ischemia.[10] Further the hydroxyl radical scavenger mannitol[11] has proved effective in reducing pulmonary injury after bilateral hindlimb ischemia in rats.[12] This study was designed to test the ability of mannitol to modify the lung injury in humans following AAA.

Materials and Methods

An open, randomized series of 26 consecutive patients undergoing elective infrarenal abdominal aortic aneurysmectomy and reconstruction with a tube graft formed the study group. Before surgery all patients had arterial and flow-directed 7 French pulmonary arterial catheters (Ab-

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bott Critical Care Catheters, N. Chicago, IL) inserted. General anesthesia was used after intramuscular premedication with 0.04 mg/kg medazolam or 0.14 mg/kg morphine sulphate. All patients were paralyzed and mechanically ventilated. They were maintained with fentanyl, oxygen, and nitrous oxide. After induction of anesthesia, crystalloid was infused to maintain a high PAWP between 10 and 12 mmHg, a technique shown to prevent large fluctuations in cardiac output during surgery.[13] Each patient received 5000 μ heparin intravenously just before application of the aortic cross clamp. An average of 0.5 units of packed red cells was transfused during aortic clamping. The remaining blood, including cell-saver blood (Autotrans, Electromedics Inc., Englewood, CO), was given at the time of wound closure through a 40μ Pall filter (Pall Corp., Glenn Cove, NY). After operation patients were gradually weaned from the ventilator and all were extubated by 24 hours.

Patients were randomized to receive 0.2 g/kg mannitol (Abbott Laboratories, N. Chicago, IL) ($n = 14$) or a similar volume (30 mL) of normal saline ($n = 12$) intravenously as a short infusion just before application of the aortic crossclamp. Measurements were conducted at the following time periods: (1) before operation; (2) 10 minutes after induction of anesthesia and intubation; (3) 30 minutes after skin incision; (4) 30 minutes after aortic clamping; (5) just before declamping; (6) 3 minutes after clamp removal; (7) at wound closure; (8) hourly for 24 hours after operation.

Hemodynamics

Several variables were monitored. Central venous pressure (CVP), mean pulmonary arterial pressure (MPAP), pulmonary arterial wedge pressure (PAWP), and mean arterial pressure (MAP) were measured with strain-gauge transducers (Trantec, Model 800, Bentley Trantec, Anasco, Puerto Rico). The values were taken at end-exhalation. Pulse rate was counted from the arterial wave form. Cardiac output (CO) measurements were performed in triplicate using the thermodilution technique.

Hematology

Platelet and white blood cell counts were assayed on arterial blood using phase microscopy.

Prostanoids

Plasma concentrations of TxB_2 and 6-ketoprostaglandin(PG)$F_{1\alpha}$, the stable hydrolysis products of TxA_2 and prostacyclin, respectively, were measured with a double radioimmunoassay[14,15] using an antibody whose cross-reactivity with heterologous prostanoids was less than 1%. Blood was drawn into tubes containing ethylene diamine tetracetic acid and aspirin. The blood was centrifuged at 1500 × g for 20 minutes and the plasma was separated and stored at −20 C until assayed.

Pulmonary Function

Mixed venous and arterial blood samples were analyzed for PO_2, PCO_2, and pH using Clark and Severinghaus electrodes (Instrumentation Laboratory, Model 813, Lexington, MA). Hemoglobin and percentage of saturation were measured spectrophotometrically (Instrumentation Laboratory, Model 282) and the physiological shunt fraction (Q̇[sc]S[xsc]/Q̇[sc]T[xsc]) was calculated from the Berggren equation.[16] Peak inspiratory pressure was measured at the end of an inspiratory pause while the patient was mechanically ventilated.

Chest Radiography

Radiographs were taken before operation, 4 to 8 hours and 24 hours after operation. All postoperative films were portable and anterioposterior exposures were taken in inspiration with the patient sitting. The x-ray films were interpreted in a blinded fashion by a single roentgenologist (R.P.). The films were assessed with regard to fixed radiologic criteria for edema and each film was assigned a score of 0 to 4 with a grade of zero being normal.

To test the ability of mannitol to inhibit Tx synthesis, an *in vitro* study was conducted. Forty-five mL of blood were obtained from normal human volunteers ($n = 14$) who had not taken aspirin or other cyclooxygenase inhibitors for ten days. The blood was anticoagulated with 5mL 3.8% sodium citrate and centrifuged at 180 × g for five minutes. Platelet-rich plasma (PRP) was carefully aspirated without disturbing the lower erythrocyte layer and divided into two aliquots. One aliquot was incubated for 30 minutes at 37 C with 0.2 mL mannitol, 1 to 10^{-4} M ($n = 7$), or dextrose 1 to 10^{-4} M ($n = 7$), while the other aliquot from the same subject was incubated at 37 with 0.2 mL saline. A platelet count was performed. Duplicate 450 μl samples of treated PRP were activated in a lumi-aggregometer (Chronolog Corp., Havertown, PA) with 50 μl 1.0mM adenosine diphosphate (Calbiochem-Behring Corp., La Jolla, CA). After one minute 10 μg of ibuprofen (Upjohn Co., Kalamazoo, MI) was added to stop prostanoid synthesis. The PRP was centrifuged and the supernatant frozen for later assay of TxB_2.

Investigations using human subjects were conducted in conformity with the principles embodied in the Helsinki declaration of 1975, and were approved by the Brigham and Women's Hospital and Harvard Medical School Institutional Review Boards for Human Research.

Data are presented as mean ± standard error in tables and figures. Statistical analysis used an analysis of variance, paired and unpaired t tests, and linear regression. When multiple comparisons were performed, the Bon-

TABLE 1. *Patient Profiles*

Patient Data	Untreated	Mannitol
Number	12	14
Age	73 ± 3	74 ± 6
Sex		
Male	6	9
Female	6	5
Preoperative disease		
Hypertension	5	9
Myocardial ischemia	6	10
Obstructive pulmonary	8	9
Body weight (kg)	74 ± 10	71 ± 12
Aortic cross clamp time (min)	61 ± 15	58 ± 16

* Values are mean ± standard error.

ferroni procedure was applied.[17] Significant difference was accepted if $p < 0.05$.

Results

Patients treated with saline or mannitol were similar with respect to age, sex, body weight, past medical history, and aortic crossclamp time (Table 1). In saline-treated patients, TxB_2 rose from preoperative values of 124 ± 24 pg/mL to 290 ± 68 pg/mL ($p < 0.01$) 30 minutes after aortic occlusion (Fig. 1). At this time there were also increases in MAP from 85 ± 5 to 103 ± 4 mmHg ($p < 0.01$), MPAP from 19 ± 2 to 27 ± 4 mmHg ($p < 0.01$; Fig. 2), and PAWP from 12 ± 2 to 15 ± 2 mmHg ($p < 0.01$). The CO fell from 6.3 ± 0.4 to 3.9 ± 0.8 L/min ($p < 0.01$; Fig. 3). Immediately after aortic occlusion sodium nitroprusside 10 to 30 μg/min was infused into 8 of 12 patients treated with saline. This lowered systemic blood pressure to 88 ± 4 mmHg. At this point CO and MPAP were unchanged. After 30 minutes MPAP had decreased to preclamping levels. In addition white blood cell counts fell from a baseline value of 9800 ± 890/mm^3 to 7600 ± 900/mm^3 ($p < 0.01$; Fig. 4) and platelets fell from 294 ± 25 to 214 ± 43 × 10^3/mm^3 ($p < 0.01$). Hematocrit decreased from preoperative values of 36 ± 4 to 31 ± 3% ($p < 0.01$) due largely to the crystalloid infusion (Table 2).

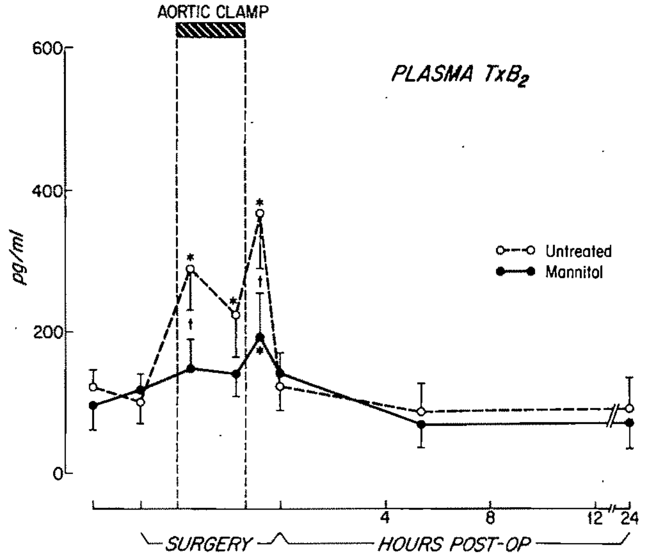

FIG. 1. Aortic crossclamping and clamp removal led to transient increases in plasma TxB_2 levels. Mannitol did not alter baseline plasma TxB_2 levels but reduced ischemia-induced TxB_2 synthesis. Asterisks and daggers refer to significance relative to baseline and between groups, respectively.

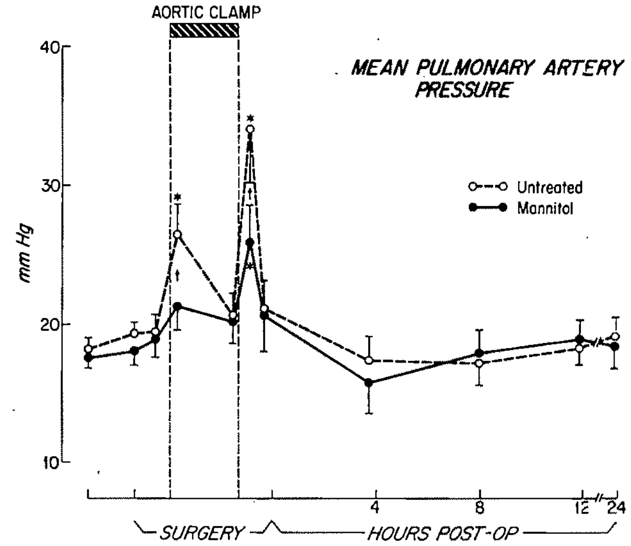

FIG. 2. Mean pulmonary artery pressure rose with aortic clamping and with clamp removal. These increases were blunted by treatment with mannitol before aortic occlusion. Asterisks and daggers refer to significance relative to baseline and between groups, respectively.

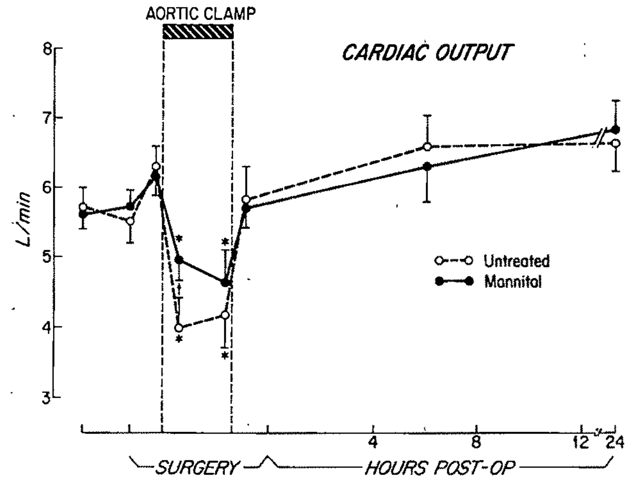

FIG. 3. Cardiac output fell with application of the aortic crossclamp and returned to normal after surgery. Mannitol reduced the magnitude of the fall in cardiac output during aortic occlusion. Asterisks and daggers refer to significance relative to baseline and between groups, respectively.

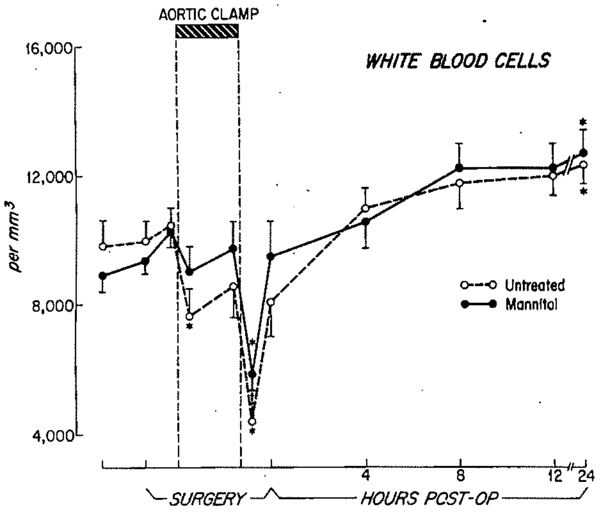

FIG. 4. Transient leukopenia occurred with aortic occlusion and with clamp removal. Mannitol prevented the clamp-induced leukopenia but only attenuated the fall in WBC counts on declamping. Asterisks and daggers refer to significance relative to baseline and between groups, respectively.

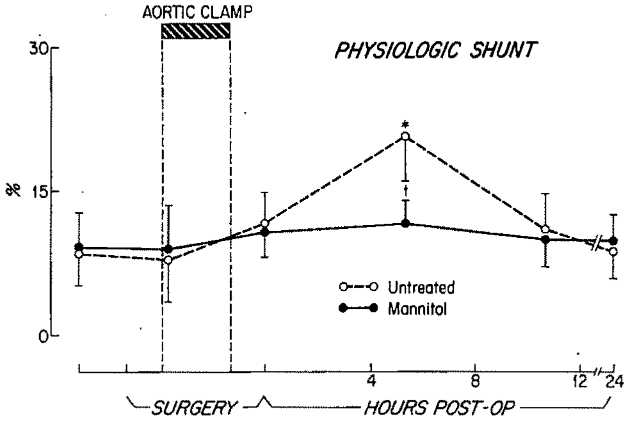

FIG. 5. Postoperative pulmonary dysfunction was manifested by an increase in physiologic shunt four to eight hours after surgery. Mannitol maintained oxygenation. Asterisks and daggers refer to significance relative to baseline and between groups, respectively.

Removal of the aortic crossclamp restored full perfusion to the lower torso. This led to a further increase in TxB_2 levels to 378 ± 105 pg/mL, ($p < 0.01$; Fig. 1) and MPAP to 34 ± 4 mmHg, ($p < 0.01$; Fig. 2). Within 30 minutes of declamping, plasma TxB_2, MPAP and CO had returned to pre-crossclamping levels. MAP and PAWP were not significantly altered during reperfusion. White blood cell and platelet counts fell further during the first ten minutes of reperfusion to 4400 ± 620/mm^3 and 125 ± 13 × 10^3/mm^3, respectively (both $p < 0.01$). The hematocrit was unchanged.

Pulmonary dysfunction occurred in all patients 4 to 8 hours after surgery. This dysfunction was manifested by increases in $\dot{Q}$[sc]S[xsc]/$\dot{Q}$[sc]T[xsc] from 9 ± 2 to 20 ± 6% ($p < 0.01$; Fig. 5) and PIP from 22 ± 2 to 32 ± 2 cm H_2O ($p < 0.01$; Fig. 6). Pulmonary edema was noted in all patients who had chest radiographs 4 to 8 hours after operation: one grade 1, four grade 2, three grade 3, and two grade 4. At this time PAWP was 12 ± 2 mmHg and CO 6.5 ± 0.5 L/min.

Nine of the 14 patients receiving mannitol required a short sodium nitroprusside infusion after aortic occlusion. As in the saline-treated group, MAP was the only variable affected during the infusion. Mannitol treatment before crossclamp application reduced the rise during aortic occlusion and declamping of plasma TxB_2 to 155 ± 55 pg/mL and 198 ± 75 pg/mL, respectively (both $p < 0.01$ relative to saline treatment; Fig. 1); MPAP to 21 ± 2 and 26 ± 3 mmHg respectively, (both $p < 0.01$; Fig. 2). In addition mannitol lessened the decline in CO to 4.9 ± 0.4

TABLE 2. *Fluid Balance*

	Saline	Mannitol
Estimated blood loss	1.7 ± 0.6	1.8 ± 0.2
Intraoperative fluid		
Autologous blood	1.2 ± 0.4	2.0 ± 0.3†
Homologous blood	0.4 ± 0.2	0.5 ± 0.3
Crystalloid	6.4 ± 1.3	6.0 ± 1.4
Colloid‡	0.8 ± 0.3	1.0 ± 0.4
Urine output	0.8 ± 0.1	0.7 ± 0.1
Postoperative fluid		
Crystalloid	4.5 ± 1.2	3.9 ± 1.6
Colloid‡	0.2 ± 0.1	0.3 ± 0.1
Urine output	4.3 ± 1.3	4.2 ± 1.6
Weight gain at 24 hours (kgs)	6.4 ± 0.8	6.6 ± 1.3

* All measurements are in litres unless otherwise stated.

† This value was significantly ($p < 0.05$) higher than the saline group.

‡ These solutions included: salt poor albumin, fresh frozen plasma and plasmanate.

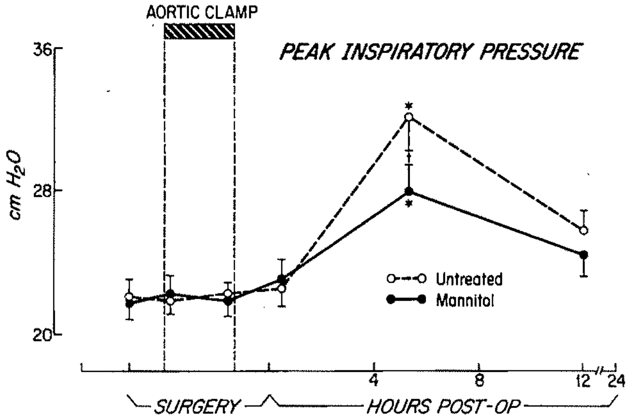

FIG. 6. Decreased postoperative lung compliance was indicated four to eight hours after surgery by an increase in peak inspiratory pressure. Mannitol reduced the ventilation pressures during the period of respiratory dysfunction. Asterists and daggers refer to significance relative to baseline and between groups, respectively.

L/min, ($p < 0.01$; Fig. 3), and white blood cell count to 5850 ± 460/mm^3 ($p < 0.01$) on declamping (Fig. 4). The postoperative rise in $\dot{Q}$[sc]S[xsc]/$\dot{Q}$[sc]T[xsc] and PIP was reduced to 12 ± 2% and 28 ± 2 cmH$_2$O, respectively (both $p < 0.01$; Figs. 5 and 6). Chest radiography revealed no pulmonary edema in the 11 patients who had chest radiographs four to eight hours after operation (n=11).

In vitro incubation of mannitol in a range of 1 to 10^{-4} M with PRP prevented TxB$_2$ synthesis in a dose-dependent manner. An equiosmolar solution of dextrose in a similar concentration range was ineffective in preventing Tx synthesis (Fig. 7).

Discussion

This study confirms recent observations that the reperfusion of ischemic tissue during AAA leads to intraoperative pulmonary hypertension, postoperative shunting, increased inspiratory pressure, and pulmonary edema.[1] In animal studies the injury is associated with the entrapment of neutrophils in pulmonary capillaries.[18] Pulmonary edema, although often due to cardiac failure and increased hydrostatic pressure in the pulmonary microvasculature,[19] has been increasingly associated with increased microvascular permeability in settings such as complement activation, aspiration, and oxygen toxicity.[20–22] The noncardiogenic nature of the pulmonary edema following lower torso ischemia and reperfusion was documented in a previous patient study[1] and was again noted here by the finding that PAWP was within normal limits before and during the time that edema was noted. The relationship between lower torso ischemia and increased pulmonary microvascular permeability has also been studied in sheep using the chronic lung lymph fistula preparation with an inflated left atrial balloon.[3] Reperfusion after two hours of bilateral hindlimb tourniquet ischemia led to a sustained increase in lung lymph flow and an increase in the lymph/plasma (L/P) protein ratio, changes that document increased permeability.

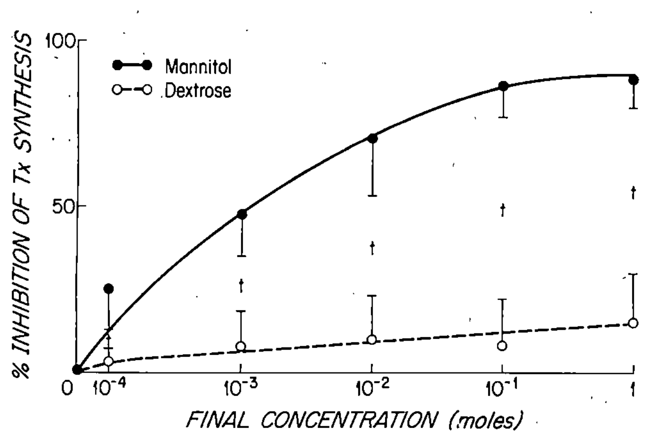

FIG. 7. Mannitol inhibited Tx production by ADP-stimulated platelets in a dose-dependent manner. An equiosmolar solution of dextrose was ineffective. Daggers refer to significance between groups.

In these sheep studies, pulmonary endothelial injury with increased permeability occurred immediately on reperfusion. In the present study pulmonary edema accumulated slowly, its rate of appearance being determined by the imbalance in transvascular fluid efflux and lymphatic clearance. This is probably the reason for the delay in respiratory dysfunction, the rise in $\dot{Q}$[sc]s[xsc]/$\dot{Q}$[sc]t[xsc] and PIP being noted only after four to eight hours (Figs. 5 and 6).

Mannitol's effectiveness in preventing the ischemia-induced lung injury in this setting is most likely due to its ability to decrease ischemia-induced Tx synthesis (Fig. 7). Tx appears to be the central mediator involved. The increase in plasma TxB$_2$ temporally correlates with the observed pulmonary hypertension in this study, while the increase in lung lymph TxB$_2$ in animal studies correlates with the increase in pulmonary microvascular permeability.[3] In addition inhibition of Tx synthesis or blockade of Tx receptors prevents the pulmonary hypertension, transient leukopenia, lung leukosequestration, and increase in lung microvascular permeability following lower torso ischemia.[3] Finally infusion of a Tx mimic has been shown to lead to increased permeability in the lungs.

Mannitol inhibits Tx synthesis, as evidenced by the findings in this study of a dose-dependent lowering of Tx production by ADP-stimulated platelets (Fig. 7). This effect may be direct or indirect by the scavenging of free radicals required for Tx synthesis.[24] Thus mannitol is a known scavenger of the OH radical[11] generated with reperfusion of ischemic tissue.[25] In addition mannitol, by scavenging oxygen-free radicals, can prevent their stimulating arachidonic acid breakdown that will lead to a general increase in eicosanoid synthesis. Thus, in addition to a rise in TxB$_2$ after ischemia, we have reported a rise in plasma leukotriene B$_4$.[26]

Oxygen-free radicals have been implicated as a cause of the local damage following ischemia in a number of tissues.[6–9] They may also mediate, in part, the pulmonary injury following remote ischemia.[10] This thesis is consistent with the beneficial effects of mannitol, as is the animal studies showing that allopurinol, and superoxide dismutase with catalase, protect sheep from lung injury after hindlimb ischemia.[10] The interpretation of the effects of the free radical scavengers is obscured by the ability of SOD to also inhibit Tx synthesis.[27] Dispite these considerations, the fact that a Tx-receptor antagonist prevents an experimental increase in pulmonary permeability after ischemia is strong evidence against the intermediary role of free radicals. It is possible, however, that the final injurious pathway after the presumed Tx activation of neutrophilis is their release of these vasotoxins. Thus mannitol inhibits the ischemia-induced neutrophil oxidative burst and consequent H_2O_2 production.[12]

The importance of white blood cells in this setting is emphasized by the protection afforded by rendering animals neutropenic before ischemia.[4] Animal studies indicate that the transient leukopenia on reperfusion and neutrophil activation is Tx dependent.[28] We believe that the subsequent entrapment of PMN in the lungs is also Tx dependent. Thus inhibition of Tx synthesis or blockade of Tx receptors not only prevents leukopenia and the oxidative burst of the neutrophil but also abolishes later pulmonary leukosequestration.[3] In rats subjected to bilateral hindlimb ischemia, mannitol reduces Tx synthesis, PMN activation, lung leukosequestration, and pulmonary injury (unpublished data). The present study suggests that by limiting the rise in Tx, mannitol can moderate the fall in circulating white blood cells (Fig. 4).

Although an osmotic control solution was not infused in this study, the observed effects of mannitol are unlikely to be due to hyperosmolarity or an intraoperative diuresis because urine output and weight gain were the same for the study and control group (Tables 1 and 2). Further in rats equiosmolar sugar solutions have proved ineffective during ischemia, in contrast to mannitol in inhibiting Tx synthesis (Fig. 7).

The lung injury following abdominal aortic aneurysmectomy is prevented by mannitol, probably by its ability to inhibit ischemia-induced Tx synthesis.

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Book Reviews

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Surgery of the Oesophagus. Glyn G. Jamieson. 934 pp. Naperville, IL: Churchill Livingstone, 1988. $195.00.

THIS BOOK IS OBVIOUSLY an effort to "cover the oesophagus" and to this end I believe the authors have been successful.

Do not let 124 contributors, of national and international reputation, and 934 pages consisting of 14 sections and 105 chapters frighten you from this reference text. The final measurement of this 5.5 cm thick book is a price of $195.00.

All the sections have their strengths and weaknesses. I found the historic section interesting and the anatomy section complete and very helpful. The radiologic section is also excellent. Throughout the book the drawings and tables included in the various chapters are more than adequate. The x-ray examples that were chosen to illustrate the variety of conditions in general are excellent. As would be the case in a reference text like this, many aspects of the pre- and postoperative care, although covered, were done somewhat superficially. Problems with regard to hiatal hernia are well presented and the operative repair section is certainly complete. I found the discussion on motility disturbances to be an outstanding section. The review of the problem of carcinoma of the oesophagus was certainly as complete and up to date as one could find in a text of this type.

I doubt this book should find its way into the hands of every student or resident. However it is an outstanding addition to the library and an excellent reference book to begin a review of any clinic problem involving the oesophagus. With 124 contributors it will be possible for most of us to know one of the authors and therefore be able to borrow his copy when appropriate.

WALTER G. WOLFE, M.D.
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Decision Making in Surgery of the Chest. Laurens R. Pickard. 168 pp. Philadelphia: W. B. Saunders, 1989. $75.00.

THIS IS AN OUTSTANDING text for thoracic surgical residents. Decision making in thoracic surgery is one of the more difficult areas to teach in thoracic surgery and is an area that is influenced greatly by training, length of experience, last antidotal case, and is generally taught to residents by example and basic information about the disease process. As we all know, the "perfectly logical" steps to making a correct surgical decision in one physician's mind are not necessarily logical in another. Dr. Pickard has accumulated a large number of experts to format the decision-making process in selected areas of thoracic and cardiovascular surgery. The contents touch on the more common congenital defects as well as acquired heart disease. Included also are rhythm disturbances, diseases of the pericardium, aorta, mediastinum, lung, pleura, chest wall, diaphragm, airway, esophagus, trauma, and pre- and postoperative care. Although not all the areas in thoracic and cardiovascular surgery are treated, the mechanism for making a surgical decision may well be helpful for those disease processes not included in the book.

When one first approaches this type of format, there is a natural resistance to line charts that refer you back to short definitions or modifiers. And, on first glance, one takes the position that this is nonsense, a waste of time. Initially the text and line charts are not easily perceived. After the second or third page into the book, the reader becomes involved in the decision-making process with the number of options available and is quite enthralled with the ability to see those decisions made in a concise, clear format. The biggest drawback to the book is getting started. I believe that this is the first step toward an interactive video disc for teaching residents decision making in thoracic and cardiovascular surgery, which may be even more useful in training residents to understand the disease process and develop a method of taking the next logical step.

This text represents a tremendous amount of work and thought and is clearly a first step in trying to understand how we make decisions and teach residents the science and art of thoracic surgery. I would suggest that this is a vital text for the cardiothoracic library and would encourage residents and faculty to explore the mechanics and format of this text.

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CALIFORNIA Coastal Community: Multi-specialty group of 44 physicians has an opening for a General Surgeon to join two surgeons in an expanding, busy, group practice. This opportunity is located in a moderate sized city with sunny beaches and excellent opportunities for outdoor activities, 25 miles south of Santa Barbara and 60 miles north of Los Angeles. Compensation is competitive. Fringe benefits are excellent. Shareholdership possible after one year. For information, contact **Recruitment Director, 2705 Loma Vista Road, Ventura, CA 93003.**

GENERAL SURGEON—Opportunity to join four physician general and vascular surgery practice in eastern Washington. Well-established, referral-based practice serving four hospitals. We are seeking an associate who is board certified or board eligible. Vascular training desirable but not required. Competitive salary with incentive bonus leading to partnership opportunity. Interested physicians please send **CV to Box ANN12D c/o J. B. Lippincott Company, East Washington Square, Philadelphia, PA 19105.**

GENERAL SURGEON: Permanente Medical Group in Fairfield, California is seeking a BE/BC General Surgeon with vascular training to join a very busy surgical department supporting a 56 member multi-specialty group. The practice is challenging, the salary and benefits are excellent. Fairfield is located within an easy commute distance from the San Francisco Bay Area or the Napa Valley, and within a 1 1/2 hour drive to the Sierra Ski slopes. Send C.V. to **Richard Holmes, M.D., 1550 Gateway Boulevard, Fairfield, CA 94533.**

GENERAL SURGERY PGY-4/PGY-5—Unexpected openings in University program. Start date: July 1, 1990. Loma Linda University Medical Center, Room 2573. **11234 Anderson Street, Loma Linda, CA 92350. (714) 824-4335.**

COLORADO PERMANENTE MEDICAL GROUP is an expanding multispecialty prepaid group practice caring for members of the Kaiser Foundation Health Plan. Position available immediately for BE/BC general surgeon to join existing eleven physician department. Competitive salary and benefits. Contact: **V. A. LaFleur, M.D., Associate Medical Director, Colorado Permanente Medical Group, P.C., 2045 Franklin Street, Denver, CO 80205, (303) 861-3263.** EOE.

FELLOWSHIP—G.I. SURGEON—Ohio Digestive Disease Institute: Opportunity for additional training in surgery of liver, biliary tract, pancreas, esophagus, stomach, and colon for board eligible general surgeon. Rotation through active G.I. diagnostic and procedure laboratory includes endoscopy, colonoscopy, ERCP, gastric analysis, and manometry and motility testing. Exposure to laboratory research as desired. For further information contact: **E. Christopher Ellison, M.D., Ohio Digestive Disease Institute, Grant Medical Center, 111 S. Grant Ave., Columbus, OH 43215.**

General/Vascular Surgeon with vascular fellowship to join three surgeons in practice of General, Vascular and Thoracic Surgery in Southern New Jersey, close to Philadelphia and shore points. Benefits and salary leading to partnership opportunity. Send CV to **Box ANN12B, J. B. Lippincott Company, East Washington Square, Philadelphia, PA 19105.**

GENERAL and non-cardiac thoracic surgery BE/BC to join multispecialty group located in a modern city nestled amongst the picturesque Blue Ridge Mountains of Virginia. There are numerous recreational opportunities summer and winter. The group practices primarily at two acute care facilities, both with trauma center designation. The group includes two vascular and one thoracic surgeon plus eight other general and specialty surgeons. Bonus at sign up if no recruiting firm involved. Apply to **Box ANN12A, J. B. Lippincott Company, East Washington Square, Philadelphia, PA 19105.**

GENERAL SURGEON desired for outstanding opportunity to associate with three colleagues in an accredited multispecialty group. Drawing area nearly 400,000 with two modern hospitals. Stimulating Big-10 University community of 110,000 with superb cultural advantages. Ideal for families. Medical School teaching affiliation if desired. Initial guarantee and fringes with early associateship and subsequent income based on productivity. Send CV to **Medical Director, Christie Clinic, 101 W. University, Champaign, IL 61820.**

GROUP HEALTH COOPERATIVE OF PUGET SOUND, a 365,000-member prepaid group practice, currently has a position available for a General and Vascular Surgeon. Referral only practice in a multi-specialty organization. To inquire, write: **Manager of Medical Staff Personnel-AS, 521 Wall Street, Seattle, WA 98121.**

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MENDOCINO COUNTY—Immediate opening in beautiful coastal northern California for full-time BC/BE general surgeon with trauma experience. Send CV to **Julie Campbell, Mendocino Coast District Hospital, 700 River Drive, Fort Bragg, CA 95437 or call (707) 961-1234.**

ONCOLOGIC SURGEON—Multi-specialty group in Suburban Philadelphia needs a BE/BC Oncologic Surgeon for clinical practice. Preference given to candidates with thoracic and vascular expertise. Endoscopic skills also desired. Excellent benefits and salary leading to full partnership position. Send Curriculum Vitae and references to **Surgical Services, Ltd., Moss Plaza, Suite 206, 9892 Bustleton Avenue, Philadelphia, PA 19115. Attention: Robin E. Rosenberg, M.D.**

Physicians needed, all specialties, for permanent employment opportunities in VA, WV, MD and states throughout the sunbelt through Physician Registry Network (PRN). PRN is a service sponsored by SunHealth participating hospitals at no cost or obligation to physicians. Please send your CV and geographic preferences to: **PRN, 9040 Roswell Road, Suite 720, Atlanta, GA 30350. Call 1-800-333-3914.**

RESEARCH FELLOWSHIP: Research Fellowship in thoracic oncology available for two to three years. Projects include the immunology and molecular biology of lung cancer and studies on molecular mechanisms of lung cancer progression. Salary is supported by an NIH Training Grant. Applicants must be U.S. Citizens or permanent residents enrolled in a General or Thoracic Surgery Residency Program. Send curriculum vitae and three references to **Dr. Jack A. Roth, Chairman, Department of Thoracic Surgery, Box 109, University of Texas M.D. Anderson Hospital and Tumor Institute, 1515 Holcombe Blvd., Houston, Texas 77030.** An Equal Opportunity/Affirmative Action Employer.

TRANSPLANTATION FELLOWSHIP: Two-year Clinical Fellowship in multiorgan transplants available to Board eligible or certified surgeons for January or July 1990. A comprehensive experience in the perioperative care of the transplant patient with broad exposure to renal, pancreatic, hepatic and multivisceral transplants. Applicants send CV and letter of inquiry to **Dr. Thomas Starzl, University of Pittsburgh, 5C Falk Clinic, 3601 Fifth Avenue, Pittsburgh, PA 15213.**

TRAUMA DIRECTOR & ASSISTANT DIRECTOR OF SURGERY: San Joaquin General Hospital, a university affiliated teaching hospital, seeks a Trauma Surgeon to direct trauma program development. In addition, the individual would serve as Assistant Director of Surgery for the Surgery Residency Program. Applicants must be Board Certified or Board Eligible. Vascular Surgery training or experience would be beneficial. Responsibilities include patient care, teaching surgical residents and administration. Excellent financial package. Send all inquiries and CV to: **Nathan M. Matolo, M.D., Chairman, Department of Surgery, San Joaquin General Hospital, P.O. Box 1020, Stockton, CA 95201, (209) 468-6600.** San Joaquin General Hospital is an Affirmative Action/Equal Opportunity Employer.

TRAUMA FELLOWSHIP: Eastern Virginia Medical School, Department of Surgery, Division of Trauma/Critical Care—The Department of Surgery of Eastern Virginia Medical School and the Shock Trauma Center/Sentara Norfolk General Hospital are accepting applications for a one year Trauma and Critical Care Fellowship commencing July 1, 1990. Applicants must have completed a residency program in General Surgery with education and experience in the field of Trauma/Critical Care. Applicants must be Board certified or eligible. The fellowship will be based at Sentara Norfolk General Hospital, the designated Level I adult/pediatric regional trauma and burn facility which has approximately 1,700 trauma/burn admissions per year. The one year program will provide significant operative and critical care experience along with an opportunity for involvement with ongoing clinical research. Applicants should send a letter of application, curriculum vitae and the names of three references to: **L.D. Britt, M.D., M.P.H., Chief, Division of Trauma and Critical Care, Eastern Virginia Medical School, Medical Director, Shock Trauma Center, Sentara Norfolk General Hospital, 825 Fairfax Avenue, Norfolk, VA 23507.**

VASCULAR ASSOCIATE: Multi-specialty surgical group in Philadelphia suburbs seeking a Vascular Associate.—Must be BC/BE—Prefer Fellow finishing now or recent graduate: Excellent benefits: Eventual partnership. Send reply to: **Vicki Robbins, Surgical Services, Ltd., Moss Plaza, 9892 Bustleton Ave., Suite 206, Philadelphia, PA 19115.**

VIRGINIA/NORTH CAROLINA—Outstanding opportunities for BC/BE General Surgeons in communities near major metropolitan areas. Financial guarantees. Send CV to: **Janet Clayton, AM Care, P.O. Box 51068, Durham, NC 27717; or call 919-490-1707.**

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WANTED: Board eligible or Board certified general surgeon with subspecialty in vascular surgery to join a three man surgical practice in Upstate New York. Send C.V. to **Surgical Associates, P.C., 161 Riverside Drive, Binghamton, NY 13905.**

PRACTICES FOR SALE—Assume an existing practice available in most states and all specialties. Practices appraised on-site. Fees paid by seller. Contact Dave Oberstein, **Jackson & Coker, 400 Perimeter Center Terrace, Suite 760 ASPB9. Atlanta, GA 30346, Tel 1-800-544-1987.**

April 20-21, 1990: Vascular Trauma: Diagnosis and Management. Postgraduate course, sponsored by Department of Surgery, University of Florida Health Science Center Jacksonville, Florida and the Florida Vascular Society, at the Jekyll Island Club Hotel, Jekyll Island, Georgia. For information contact **Alicia Azouz, CME Coordinator, UFHC/J, 580 W. 8th Street, Jacksonville, Florida 32209, (904) 359-6510.**

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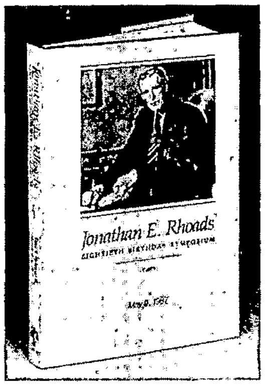

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Steven A. Rosenberg, M.D., Ph.D.
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